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Review

Platelet-rich plasma (PRP) in nerve repair

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ABSTRACT

Platelet-rich plasma (PRP) has the capability of assisting in the recovery of damaged tissues by releasing a variety of biologically active factors to initiate a hemostatic cascade reaction and promote the synthesis of new connective tissue and revascularization. It is now widely used for tissue engineering repair. In addition, PRP has demonstrated nerve repair and pain relief, and has been studied and applied to the facial nerve, median nerve, sciatic nerve, and central nerve.

These suggest that PRP injection therapy has a positive effect on nerve repair. This indicates that PRP has high clinical value and potential application in nerve repair. It is worthwhile for scientists and medical workers to further explore and study PRP to expand its application in nerve repair, and to provide a more reliable scientific basis for the opening of a new approach to nerve repair.
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Abbreviations: PRP, Platelet-rich plasma; ADSCs, dipose-derived stem cells; COL/CS, collagen/chitosan; CTS, Carpal tunnel syndrome; CNS, Central nervous system; AD, Alzheimer's disease; MPG, Major pelvic ganglion; CXCL5, Cys-X-Cys motif chemokine ligand 5; CXCR2, Cys-X-Cys chemokine receptor 2; RGCs, retinal ganglion cells.

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1. Introduction

Nerve injuries have caused many pains, and even disabilities, in humans and economic losses [1–3]. Currently, nerve repair is primarily depended on microsurgical procedures such as in situ suturing and autologous nerve grafts [4]. Surgical procedures can be performed to realign damaged nerves by approaching the end or implanting a graft, but these procedures may be limited by the location of the injury and the length of the graft required, resulting in suboptimal recovery [4]. However, platelet-rich plasma (PRP) has significant therapeutic potential as a neuroprotective, neurogenic and neuroinflammatory therapeutic modifier system [5,6]. In addition, PRP and its growth factor mixtures have shown exciting nerve regeneration and analgesic abilities [7]. The basic principle of PRP therapy is to inject concentrated platelets at the site of injury to initiate tissue repair by releasing a variety of bioactive factors (growth factors, cytokines, lysosomes) and adhesion proteins, which are responsible for initiating the hemostatic cascade reaction, synthesis of new connective tissues, and revascularization [8]. PRP can promote nerve regeneration [9], and the mechanism may be that various endogenous and exogenous activating substances promote platelet activation after an injury to the organism, the α-granules in platelets undergo a degranulation reaction, releasing a large amount of growth factors, fibrinogen, tissue protease and hydrolases [10,11]. The released growth factors bind to the outer surface of the cell membrane of the target cell via transmembrane receptors on the cell membrane. These transmembrane receptors in turn induce the activation of endogenous signaling proteins that further activate intracellular second messengers. The latter induce various intracellular gene expressions such as cell proliferation, matrix formation and synthesis of collagen [12]. There is evidence that cytokines released by platelets, as well as other transmitters, play an essential role in reducing or eliminating chronic neuropathic pain [13] (see Tables 1–4).

Therefore, PRP is considered a prospective product for the treatment of peripheral nerve regeneration after nerve injury [14]. Many doctors and researchers have been intrigued by the therapeutic effects and applications of PRP in nerves. This article assembles the effects or applications of PRP in various nerve repairs (Fig. 1), aiming to help readers more rapidly visualize the applications of RPP in nerve repair.

2. PRP in facial nerve injury repair

Peripheral facial nerve palsy is a devastating disease with unavoidable residual sequelae due to poor functional recovery after facial nerve damage [15,16]. Although extraneural and nerve bundle sutures are the most widely used repair techniques, there is still room to improve their clinical efficacy [17]. For example, combined PRP treatment and repair of the facial nerve may be an alternative modality with better clinical outcomes [18,19].

Sun et al. used 32 New Zealand big-eared white rabbits to produce a model of a 1 cm-long defect in the left facial nerve. This study demonstrated that composite adipose-derived stem cells (ADSCs) can survive as seed cells in vivo. ADSCs can be differentiated into Schwann cell-like cells under PRP induction, and can be combined with decellularised allogeneic nerves for repairing peripheral nerve injury in rabbits with good effect [18].

Li et al. demonstrated the protective effect of PRP on traumatic facial nerve injury through rat experiments. Possible mechanisms include inhibition of platelet-activated growth factor activation, production of inflammatory mediators, and up-regulation of neurotrophic factors [20]. This group's subsequent research showed that PRP could promote the recovery of nystagmus, eyelid closure, and electrophysiological functions in nerve crush-injured rats [21]. PRP can release growth factors, including nerve growth factors and brain-derived neurotrophic factors. Furthermore, the S-100 protein expression level was higher in the PRP experimental group, all of these factors are in favor of facial nerve injury repair [21].

Şahin et al. showed that PRP enhances the positive effects of chitosan gel on facial nerve healing through rat experiments [19]. Farrag et al. showed that PRP had a measurable neurotrophic effect on facial nerve regeneration after transection in a rat model. Moreover, the number of axons was revealed to be higher in the PRP experimental group in histology, which further validated the neurotrophic effect of platelet growth factor on neurons [22].

As a result, PRP offers more possibilities to enhance the clinical outcome of suture repair of the facial nerve. It is a new direction for future clinical trials and research.

3. PRP in median nerve injury repair

Carpal tunnel syndrome (CTS) is one of the diseases in which the median nerve is damaged [23]. Because of the nerve regeneration and analgesic ability of PRP and its growth factor mixtures, it might be possible to accelerate the repair of the median nerve, alleviating the patients' pain, and promoting the recovery of patients through PRP-assisted surgical and conservative treatment of CTS [24–26]. Many experts and scholars have further explored in this area.

Gao et al. compared corticosteroids, 5% glucose and PRP injections for the treatment of CTS by meta-analysis and concluded that PRP injection was the most recommended treatment [24].

By injecting PRP into a rabbit model of glucose-induced median nerve injury, Park et al. [27] observed significant improvement in electrophysiological and histological findings after 12 weeks compared to the previous ones, which indicated that PRP injection

Table 1
Mechanisms of PRP repair in the facial nerve.

Author	Year	Subject (of an experiment)	Injection	Possible mechanisms	Refs
Sun et al.	2018	New Zealand big-eared white rabbits	CM-Dil-ADSCs composite xenogeneic nerve + autologous PRP	ADSCs can be differentiated into Schwann cell-like cells under PRP induction, and can be combined with decellularised allogeneic nerves for repairing peripheral nerve injury.	[18]
Li et al.	2019&2023	Female Wistar rats	Allogeneic PRP	PRP can release growth factors, including nerve growth factors and brain-derived neurotrophic factors.	[20,21]
Şahin et al.	2022	Male Wistar albino rats	Allogeneic PRP + chitosan	PRP can enhance the effect of chitosan, possibly by releasing a variety of growth factors, such as PDGF, transforming growth factor B, and vascular endothelial growth factor.	[19]
Farrag et al.	2007	Male Sprague-Dauley rats	Allogeneic PRP	PRP promotes axonal regeneration by releasing growth factors.	[22]

Abbreviations: PRP, platelet-rich plasma; ADSCs, adipose-derived stem cells; PDGF platelet-derived growth factor.

Table 2
Mechanisms of PRP repair in the median nerve.

Author	Year	Subject (of an experiment)	Injection	Possible mechanisms	Refs
Park et al.	2014	Male New Zealand white rabbits	Autologous PRP	PRP may inhibit collagen remodeling and vascular proliferation in the subsynovial connective tissue in the carpal tunnel.	[27]
Ran et al.	2022	Patient with distal radius fracture combined with median nerve injury	Autologous PRP	PRP can stimulate the regeneration of endovascular and trophoblastic arteries, enhance the effect of axoplasmic transfer of trophic factors, and provide nutrients for cell proliferation and neural axon growth. At the same time, PRP contains a high concentration of leukocytes and most of the bacteriostatic proteins, which can inhibit the growth of bacteria and reduce the inflammation of the local area.	[26]

Abbreviations: PRP, platelet-rich plasma.

Table 3
Mechanisms of PRP repair in the sciatic nerve.

Author	Year	Subject (of an experiment)	Injection	Possible mechanisms	Refs
Yadav et al.	2022	8-week-old male Sprague Dawley rats	Autologous platelet-rich growth factor (extracted from PRP)	PRGF inhibits pro-inflammatory cytokines during M1 macrophage induction and suppresses M1 macrophages by modulating the inflammatory microenvironment. It also promotes nerve regeneration and remyelination by increasing the number of SCs, regenerating axons and remyelination.	[40]
Yuan et al.	2023	Male Sprague-Dauley rats	The COL/CS composite film + autologous PRP (surrounds the nerve anastomotic end with the COL/CS composite film after the sciatic nerve suture)	Loading PRP gel on the surface of COL/CS composite films could significantly improve the biocompatibility of films and promote the proliferation of SCs.	[42]
Zhu et al.	2020	Male New Zealand white rabbits (4-month-old healthy, clean)	Autologous PRP	PRP could significantly stimulate the proliferation and secretion of SCs and nerve repair.	[43]
Wang et al.	2022	Male New Zealand white rabbits (5-month-old; 2.5–3.5 kg)	Autologous PRP	PRP increases the expression of ITGB8, and promotes peripheral nerve regeneration after sciatic nerve injury by affecting angiogenesis and intracellular ubiquitin levels.	[44]

Abbreviations: PRP, platelet-rich plasma; PRGF, platelet-rich growth factor; COL/CS, collagen/chitosan; SCs, Schwann cells; ITGB8, integrin subunit β-8.

could effectively control the progression of median nerve injury. According to Galán's study, PRP-assisted open surgical nerve release therapy has long-term beneficial effects on pain reduction and functional improvement of nerves and neuromuscular units in patients with CTS [28].

Malahias et al. and Güven et al. demonstrated that PRP has considerable clinical efficacy in the treatment of CTS in both the short and medium term, after a single injection of PRP for 1 month in CTS patients, which resulted in a significant improvement in pain in the majority of patients [29,30]. Senna et al. reached the same conclusion and showed that PRP was superior to corticosteroids in improving median nerve pain, function and distal sensory latency [25].

Chen et al. suggested that PRP is a novel treatment for moderate to severe CTS, and ultrasound-guided single-dose peripheral nerve extranodal PRP injections were efficacious up to 1 year after injection [31]. In the study by Shen et al., lower body weight, distal motor latency, and cross-sectional area of the median nerve values at 3- and 6-month follow-up predicted a better prognosis for patients with moderate CTS after perineural injection of PRP [32].

In a study by Ran et al., it was shown that PRP was an adjunctive treatment for elderly patients with distal radius fracture with

Table 4
Mechanisms of PRP repair in the central nerve.

Author	Year	Subject (of an experiment)	Injection	Possible mechanisms	Refs
Farid et al.	2022	Male adult Persian cats (2–3 years)	Laser-activated autologous PRP	Laser-activated PRP can significantly improve locomotion and sensory activities without impairing the CNS, enhance axonal regeneration, promote remyelination, inhibit apoptosis, improve angiogenesis and immune response.	[48]
Castro et al.	2019	Female Lewis rats (LEW/HsdUnib, 8-week-old)	Autologous PRP	Platelets are possibly stimulated to release factors that interact with cells of the spinal microenvironment to improve regeneration and decrease inflammation.	[52]
Wu et al.	2020	Male Sprague-Dawley rats	Allogeneic PRP	PRP can stabilize the expression of CXCR2 and increase the expression of CXCL5 in MPG.	[54]

Abbreviations: PRP, platelet-rich plasma; CNS, central nervous system; CXCL5, Cys-X-Cys motif chemokine ligand 5; CXCR2, Cys-X-Cys chemokine receptor 2; MPG, major pelvic ganglion.

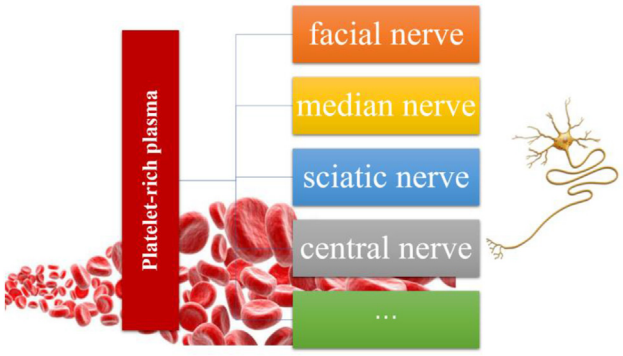


Fig. 1. Application of PRP in the repair of diverse nerve injuries.

median nerve injury, which reduced the degree of pain and improved sensorimotor function, wrist function and muscle strength [26]. However, Raeissadat et al. reported that a single injection of PRP in the wrist had no significant effect on pain and symptom severity, functional status, and electrophysiological parameters in women within a relatively short period of time after treatment, and did not increase the effectiveness of conservative treatment with wrist splinting [33]. Meanwhile, Yasak et al. demonstrated in a clinical study that a single injection of PRP had no significant effect on median nerve regeneration after CTS surgery in diabetic patients [34]. This may be owing to the poor prognosis of diabetic patients due to their concomitant growth factor deficiency and diminished immune system response [35,36]. In conclusion, PRP injections have a considerable and bright future in repairing the median nerve and assisting in the treatment of diseases and pain associated with its cause.

4. PRP in sciatic nerve injury repair

The sciatic nerve is the largest and longest nerve in the human body, innervating the popliteal, calf and foot muscles and playing an instrumental role in sensation in the calf and foot [37,38]. The sciatic nerve innervates sensory and motor functions in almost all areas below the knee joint [37,38]. Direct injury to the sciatic nerve is common not only in battle wounds [39], but also in displaced acetabular fractures or dislocation of the femoral head. PRP injection-assisted therapy may provide new therapeutic ideas for sciatic nerve repair.

Many scholars have explored this research direction of PRP repair of sciatic nerve. For example, Yadav et al. concluded that autologous platelet-rich growth factor reduces M1 macrophages and modulates the inflammatory microenvironment to promote sciatic nerve regeneration [40]. Giannessi et al. found that the application of PRP fibrin membrane around the rat sciatic nerve model improved the nerve regeneration process. In this case, PRP as a suturable membrane not only serves as a source of bioactive proteins but also as a nerve guide to control the scarring response, thus promoting axonal regeneration [41]. Yuan et al. constructed a rat sciatic nerve defect model, which demonstrated that collagen/chitosan (COL/CS) composite membranes containing PRP gels were more capable of promoting nerve regeneration and functional recovery in sciatic nerve-injured rats, suggesting that the combined application of PRP gels and COL/CS composite membranes would be a potential avenue for the treatment of peripheral nerve injury [42].

Zhu et al. showed through animal experiments that PRP at 4.5 times the platelet concentration of whole blood could significantly stimulate the proliferation and secretion of Schwann cells and promote sciatic nerve repair. This study also showed that injured nerve stiffness and changes in blood perfusion were positively correlated with the percentage of collagen area and vascular endothelial growth factor expression, respectively, and that ultrasound-guided multifrequency injections of autologous PRP were effective in the treatment of sciatic nerve crush injuries [43]. All of the above studies indicate that PRP has a positive effect on sciatic nerve injury repair. PRP affects sciatic nerve regeneration by promoting peripheral nerve regeneration after sciatic nerve injury by affecting angiogenesis and intracellular ubiquitin levels [44]. And the expression of integrin subunit β-8 (ITGB8), which is involved in angiogenesis, was increased in PRP after sciatic nerve injury [44]. Therefore, future clinical trials and studies of PRP for human sciatic nerve repair are likely to provide a better therapeutic modality for sciatic nerve injury repair in humans.

5. PRP in central nerve damage repair

Central nervous system (CNS) disorders include brain or spinal cord injuries, neurological tumors and various neurological disorders such as Alzheimer's disease (AD), Parkinson's disease, stroke and amyotrophic lateral sclerosis, all of which have a negative impact on patients' quality of life, and even threaten their lives [45,46]. The powerful restorative properties of PRP are mainly based on the neurotrophic capacity of growth factor-rich preparations and the scaffolding effect of platelet-rich gels, which can be demonstrated to ameliorate the pathological process of CNS disorders [47].

Farid et al. [48] demonstrated that PRP may have central neuroprotective and neurotrophic effects, leading to successful therapeutic results in the treatment of neurodegenerative diseases and multiple sclerosis. Animal studies by Liao et al. showed that PRP treatment significantly enhanced myelinated nerve regeneration and attenuated smooth muscle atrophy in the inferior body [49]. Other studies by this group showed that PRP also significantly increased neurofilament-1 expression, suggesting a positive effect on the CNS [50]. Salarinia et al. found that PRP injection promoted axonal regeneration in rats with spinal cord contusions. In addition, at week 5 after spinal cord injury, rats given PRP at 24 h post-injury showed significant functional recovery. This study is the first to report that PRP improves CNS recovery after spinal cord injury [51]. Castro et al. found that PRP treatment restored some of the foot and paw withdrawal reflexes in rats, indicating that primary afferent nerves re-entered the spinal cord from the dorsal root ganglion without exacerbating glial reactivity. Also, PRP treatment was shown to have immunomodulatory properties in mRNA level analysis [52]. Recently, in vitro studies on neuronal cultures from a mouse model of AD showed a dramatic reduction in neurotoxicity induced by the addition of aggregated β-amyloid to primary neuronal cultures, and an increase in the number of viable cells after co-treatment with PRP [6]. Furthermore, chronic intranasal administration of PRP-induced neuroprotection in a mouse model of AD, which may be mediated by activation of the anti-apoptotic PIEK/Akt signaling pathway [53].

The mechanism may be that PRP contains high levels of Cys-X-Cys motif chemokine ligand 5 (CXCL5). Major pelvic ganglion (MPG) neurons express CXCL5 and Cys-X-Cys chemokine receptor 2 (CXCR2). Intracorporeal injection of PRP into the corpus cavernosum stabilized the expression of CXCR2 and increased the expression of CXCL5 in MPG, thereby enhancing the neuroprotective effect [54].

Therefore, PRP treatment for CNS-type injuries can be further investigated in the clinic. This will enable PRP to provide a new therapeutic option for CNS injuries, thus helping to alleviate the pain for more patients.

6. PRP in other nerves repairs

PRP has a broad application in promoting nerve recovery, which is not only limited to the applications in the nerves mentioned in the above articles. Tai et al. [55] found that PRP effectively repaired degenerative nerves, protected the endothelial and appendage connections of smooth muscle on the body surface, and repaired axonal scaffolds by up-regulating the expression of neurofilament-H (NF–H) through animal experiments. PRP enhances neural stability by augmenting the process of axonal myelin regeneration in aged rats with erectile dysfunction [55]. In addition, electron microscopic observations showed that PRP had a protective effect on myelinated axons and prevented smooth muscle atrophy in the inferior body by maintaining adhesive connections. Wu et al. [56] and Ding et al. [57] experimentally demonstrated that cavernous injection of PRP could increase the number of myelinated axons in rats with bilateral cavernous nerve injury models and promote the recovery of erectile function.

Li et al. [58] successfully created an optic nerve clamp injury model in the right eye of New Zealand white rabbits, and their results showed that PRP could effectively inhibit the apoptosis of retinal ganglion cells (RGCs) and the secondary damage of the retina after optic nerve injury. It promotes the anti-apoptotic effect of RGCs, thus slowing down retinal and optic nerve injury after traumatic optic neuropathy. It also facilitates optic nerve and retinal repair by upregulating the expression of nerve growth factors. PRP-loaded nerve-guiding catheters provide a favorable environment for nerve regeneration and have demonstrated the therapeutic potential of this technique to promote laryngeal recurrent nerve recovery [59].

In addition, the feasibility of PRP as a potential treatment for osteodystrophic neuritis in patients with post-traumatic headaches has been assessed, providing evidence for further large-scale studies [60]. A case report of intraneural PRP injection for radial neurotomy illustrates the potential of PRP infiltration to promote the healing process of radial nerve palsy [61]. Kong et al. [62] concluded that PRP intramyofascial injection for the treatment of patients with herpes zoster has significant efficacy, which can significantly reduce the degree of pain, enhance the quality of sleep, and improve the emotional state of patients. And the therapeutic safety is great, which is worthy of clinical promotion and application. It has also been demonstrated that perineural injection of PRP is an effective therapy to relieve pain and numbness of diabetic neuropathy and enhance peripheral nerve function [63].

6.1. Limitation

This paper only reviews the repair of some nerves by PRP injections, and it does not explore the efficacy of PRP in combination with other drugs, stem cells, or physical therapies for nerve injury. Moreover, this paper also did not explore whether different preparation methods of PRP would have an effect on its efficacy.

6.2. Prospect

PRP is now widely used for tissue engineering repair [48], but it is not systematic and comprehensive enough for nerve injury treatment. The optimal injection time, frequency, and preparation method of PRP for nerve repair are also not yet standardized. Individual patient factors such as age and comorbidities may lead to differences in PRP-related growth factors and overall composition [64]. Injections of autologous products for neuropathic pain may limit adverse effects, but all these conclusions from preclinical and clinical studies need to be confirmed by further studies, especially longer observation periods [7]. However, PRP has a high clinical value and application prospect in nerve injury repair, which still deserves to be continuously explored and investigated by experts and clinicians. By further studying the clinical efficacy of PRP in different nerve injuries, it is possible to develop relevant preparation standards and efficacy evaluation standards for nerve injury treatment with PRP, and to standardize the use of PRP in the clinical setting.

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Consent for publication

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Authors' contributions

JT, ZPL, SYW contributed to the conception of the study. SYW prepares, creates, or expresses content for publication, especially writing first drafts, including substantive translations. SYW and ZPL contributed significantly to manuscript preparation. JT, ZPL, JNW and LLC prepares or presents content for publication, especially comments, annotations, or revisions, including such work that occurs before and after publication. SYW drew the figure and wrote and edited the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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