PERSPECTIVE

Platelet-rich plasma: the role in neural repair

The efficacy of platelet-rich plasma (PRP) to promote tissue regeneration has been largely confirmed in several clinical settings, such as in human maxillo-facial (Froum et al., 2002), heart (Vu et al., 2015) and orthopaedic surgery (Zhang and Wang, 2010). Up to date, few studies are available regarding the topical use of platelet-rich plasma in models of peripheral nerve injury or central nervous system pathology and the results contrasting.

Farrag et al. (2012) showed positive effects of PRP in a rat model of facial nerve regeneration with a better functional outcome with the use of PRP in comparison with no bioactive agents (platelet-poor plasma). Giannessi et al. (2014) evidenced improvement of sciatic nerve regeneration after neurorraphy when a PRP suturable membrane was applied in the lesion site, as shown by increase of fiber density.

Platelets contain the matrix proteins (fibronectin, vitronectin, and laminin). In a healing wound polypeptide growth factors identified in platelet granule, such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGFβ), through different signaling pathways, induce transcription, translation, cell division, and/or migration. Fibroblasts are drawn into the fibrin clot by PDGF and TGFβ. The fibroblasts begin to synthesize more fibronectin and also collagen, under the influence of platelet-derived serotonin and TGFβ (Dees et al., 2011). In addition, platelets induce cell proliferation (Moshiri and Oryan, 2013) and differentiation (Zhang and Wang, 2010), stimulate neo angiogenesis (Kurita et al., 2011) and vascular restoring at the site of damage (Stellos and Gawaz, 2007). The bioactive proteins control the nerve healing reducing the scar formation and supporting fiber nerve remyelination by release of large quantities of growth factors fragment, which could polymerize into platelet-rich gel with scaffolding effect (Moshiri and Oryan, 2013).

In peripheral nerve surgery, an incomplete recovery is always related to the scar formation due to epineural connective which may affect a mechanical barrier to axonal regeneration; in addition, the extraneural scarring may lead to the adhesion of nerves to adjacent tissue. Despite both surgical techniques and the understanding of nerve regeneration progressed a lot in the last decades, severe lesions of major nerve trunks still impair functionality even after surgical neurorraphy; therefore, reducing epineural and extraneural scar formation by the use of bioactive factors which regulate the connective proliferation, can perform axoplasmic migration into the distal stump improving the outcome after nerve injury.

The mechanisms whereby PRP might improve tissue healing/regeneration are still unclear, however. Data in a rat sciatic nerve model (Giannessi et al., 2014) show that the application of a PRP fibrin membrane around the neurorraphy site improves the nerve regeneration process. The use of PRP as a suturable or contact membrane could perform an action not only as a source of bioactive proteins, but also as a nerve guide to hold the scar reaction and thus improve axonal regeneration.

The only data available on the efficacy of PRP in nerve regeneration derive from animal models of peripheral nerve injury, while no study is published regarding the use of PRP in human nerve injury.

PRP extraction process is rapid, requires minimal equipment and could be applied to a patient within hours of a treatment decision. The compound is freshly prepared for each patient, so there are no problem of storage and shelf-life and, as autologous, it does no provoke an immune response in the patient and it is devoid of putative risk of infectious agent donor transmission. The high safety and the easy manageability of the product make PRP extremely advantageous in a variety of clinical settings, in hospital as well as outpatient clinics. In addition it appears of polivalent use due to its no tissue specific biological properties, differently from most of the other biomaterial or engineered

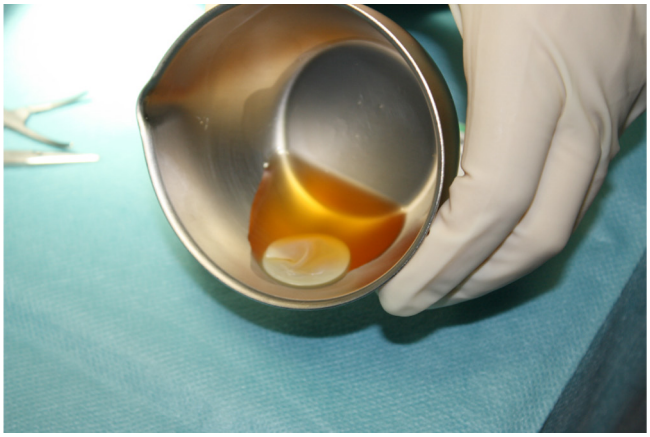

Figure 1 The final macroscopic appearance of the platelet-rich plasma (PRP) diskette obtained from centrifugation of autologous blood (standard laboratory protocol of extraction, based on Ragen Lab method and using the Extracell Membrane Kit).

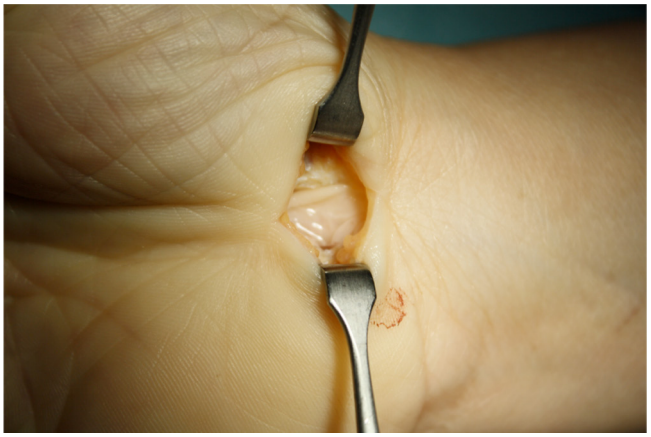

Figure 2 Platelet-rich plasma (PRP) membrane positioning during a surgical release for severe median nerve compression at the wrist.

tissue preparations currently used which are mainly strictly designed for a specific tissue target, in relation to their selective biocompatibility and mechanical properties (Siemionow et al., 2013).

The scarce regenerative capacity of damaged nerve fiber and the scar formation as inevitable result of its injury, this latter eventually enhanced by apposition of heterologous material, can detrimentally influence and restrict the creation of a neural scaffold for the regeneration. In this view and also considering absence, to date, of alternative standardized technique or material of first choice, together with current trend toward prospective, randomized, controlled clinical studies in the area will likely continue to support the use of PRP as a therapeutic agent also in peripheral nerve injury.

In their acute injury model of sciatic nerve neurotmesis in the rat Giannessi et al. (2014) based their study using electromyographic (EMG) trace, gross, and histological changes as primary endpoints in association to clinical course.

Our first data collected in a population of severe tunnel carpal syndrome patients, which received PRP application on the damaged nerve during the surgical release, corroborate the results obtained in animal models (**Figures 1** and **2**). In this perspective, future clinical trial studies should be designed to verify the real efficacy of PRP at clinical level also in regenerative medicine regarding nerve injuries.

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References

Dees C, Akhmetshina A, Zerr P, Reich N, Palumbo K, Horn A, Jungel A, Beyer C, Kronke G, Zwerina J, Reiter R, Alenina N, Maroteaux L, Gay S, Schett G, Distler O, Distler JH (2011) Platelet-derived serotonin links vascular disease and tissue fibrosis. J Exp Med 208: 961-972.

Farrag TY, Lehar M, Verhaegen P, Carson KA, Byrne PJ (2007) Effect of platelet rich plasma and fibrin sealant on facial nerve regeneration in a rat model. Laryngoscope 117:157-165.

Froum SJ, Wallace SS, Tarnow DP, Cho SC (2002) Effect of platelet-rich plasma on bone growth and osseointegration in human maxillary sinus grafts: three bilateral case reports. Int J Periodontics Restorative Dent 22:45-53.

Giannessi E, Coli A, Stornelli MR, Miragliotta V, Pirone A, Lenzi C, Burchielli S, Vozzi G, De Maria C, Giorgetti M (2014) An autologously generated platelet-rich plasma suturable membrane may enhance peripheral nerve regeneration after neurorraphy in an acute injury model of sciatic nerve neurotmesis. J Reconstr Microsurg 30:617-626.

Kurita J, Miyamoto M, Ishii Y, Aoyama J, Takagi G, Naito Z, Tabata Y, Ochi M, Shimizu K (2011) Enhanced vascularization by controlled release of platelet-rich plasma impregnated in biodegradable gelatin hydrogel. Ann thorac surg 92:837-844; discussion 844.

Moshiri A, Oryan A (2013) Role of platelet rich plasma in soft and hard connective tissue healing: an evidence based review from basic to clinical application. Hard Tissue 2:6.

Siemionow M, Uygur S, Ozturk C, Siemionow K (2013) Techniques and materials for enhancement of peripheral nerve regeneration: a literature review. Microsurgery 33:318-328.

Stellos K, Gawaz M (2007) Platelet interaction with progenitor cells: potential implications for regenerative medicine. Thromb Haemost 98:922-929.

Vu TD, Pal SN, Ti LK, Martinez EC, Rufaihah AJ, Ling LH, Lee CN, Richards AM, Kofidis T (2015) An autologous platelet-rich plasma hydrogel compound restores left ventricular structure, function and ameliorates adverse remodeling in a minimally invasive large animal myocardial restoration model: a translational approach: Vu and Pal "Myocardial Repair: PRP, Hydrogel and Supplements". Biomaterials 45:27-35.

Zhang J, Wang JH (2010) Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. Am J Sports Med 38:2477-2486.