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Prospects of the use of autologous biological materials in ophthalmology

Vasyuta V. A. [1], **Oleksenko N. P.** [2], **Medvedovska N. V.** [3]

[1] SI «Romodanov Neurosurgery Institute, National Academy of Medical Sciences of Ukraine»
Kyiv (Ukraine)

[2] National Academy of Medical Sciences of Ukraine
Kyiv (Ukraine)

Biotechnological means are under active development, and those related to the use of stem cells, biopolymer-based matrices and their combinations are especially important in the field of medicine. We believe that especially promising is the local use of patient's autologous biological materials that may significantly enhance the repair processes at the site of damage, with no risk of infection, immunological conflict, and uncontrolled biological degradation, and no ethical problems.
This is applied as a universal approach in many fields of medical practice. The potential of patient's biological materials in neurology (especially, neuroophhthalmology) is under active research. Studies have shown that platelet rich plasma (PRP) and cell-free and stem- and progenitor-cell rich PRP matrices can stimulate neural repair, preventing the loss of optic nerve functions.
Particularly, PRP-derived autologous materials, when used in retinal neuronal and optic nerve lesions of various origins, stimulate regenerative processes, with the preservation of neural cell viability, resistance to toxic exposure, and improvement in vascularization. The use of stem and progenitor cells incorporated into the matrix significantly expands it repair potential due to the direct differentiation of these cells, replacement of damaged and lost cells and release of a variety of biologically active substances directly at the site of lesion. Therefore, the data presented in this review demonstrate the viability of the use of autologous biological materials in current neuroophthalmology and the need for developing treatment protocols for particular diagnoses.

Key words:
platelet rich plasma, fibrin matrix, autologous stem cells, macular degeneration, recurrent maculopathy, optic neuropathy, retinal detachment, optic nerve, retina

Introduction

Until recently, most clinical applications of patient's own cell-free biological materials and plasma derivatives have been related only to cosmetology. Active efforts are made to apply platelet-rich plasma (PRP) and cell-free, stem-cell rich and progenitor-cell rich PRP matrices in practice of various specialties (e.g., neurology). The above materials can be obtained from the patient's own tissues, and it has been demonstrated that autologous nerve grafts or injections of autologous biological materisls can be used for repairing peripheral nerve gaps, preventing the loss of peripheral nerve functions [1-8].

The advantages of using autologous cell and cell-free materials compared to using foreign human, animal, plant or synthetic materials include biological safety, the absence of ethical issues and the absence of an immune response to their presence in the body, and controlled biodegradation without unwanted side effects.

Visual function is essential for humans, with its loss substantially affecting the quality of life. It is noteworthy that the use of autologous biomaterials for repairing the optic nerve depends on the severity of damage, disease duration, patient's age, presence of comorbidities and co-morbidity-related complications (e.g., impaired vascularization), etc.

It is this that necessitated developing a review to systematize and compare various approaches to using PRP, platelet rich fibrin (PRF) and their combinations with active substances, stem cells and progenitor cells in an attempt to restore vision in patients.

In this work, we will consider general approaches to the neural repair functions of the above materials, provide some explanations for the ways they work, and review particular cases of their successful use for optic nerve and retinal lesions of various origins.

This work will be helpful for generalizing the data available and subsequent standardizing and improving the clinical methods involving the use autologous biomaterials in ophthalmology.

Major part of the paper

The limited use of autologous biomaterials (PRP, PRF, and their combinations with active substances, stem cells

and progenitor cells) in neurological practice may be attributed to a wide-spread opinion that these materials will contribute to the development of fibrosis rather than the neural tissue. Studies of the recent decade, however, have demonstrated that such biological materials as PRP, stem cells and progenitor cells have a universal reparative effect on various body systems (including e.g., the neural system). Thus, PRP and its derivative, PRF matrix, contain a pool of trophic factors that prevent neural cell apoptosis, stimulate axonal regeneration, improve tissue blood supply by preventing glial scar formation, contribute to the revascularization of the damaged area, and stimulate Schwann cell proliferation and myelination of nerve fibers [5, 9-16]. It has been also demonstrated that endogenous stem cells (first of all, bone marrow stem cells [BMSC] and adipose derived stem cells [ADSC]) synthesize neurotrophins, have a potential for neurogenic differentiation, and stimulate endogenous Schwann cells proliferation [17-23].

Polymerized PRF has a non-rigid gel-like structure which enables wrapping the site of damage, thereby creating a microenvironment favoring regeneration [24]. Its density can be regulated by changing fibrinogen and platelet levels and through the effect on polymerization conditions [17, 25-27].

A significant clinical advantage of the use of PRF is that it can be injected in the liquid state and polymerize at the site of damage [28]. A minimally invasive administration method allows avoiding excessive complications, supporting the three-dimensional (3D) structure of the damaged tissue, and avoiding further deformation of the nerve, providing trophic support and stimulating tissue regeneration.

Trophic support derives from the trophic factors present in PRP and PRF such as nerve growth factor (NGF), brain-derived neutotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF)-1, platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), etc. [29]. Growth factors stimulate angiogenesis, cell proliferation, cell differentiation, and contribute to the development of the extracellular matrix (ECM) (that is, have a reparative and stimulating effect), which also has a significant neurotrophic potential. Moreover, fibrin matrix can be additionally supplemented with neurotrophic and neuroinductive substances, e.g., retinoic acid, which significantly improves the neuroprotective and neuroregenerative effect [30-32].

It has been demonstrated that PRP and PRF inhibited apoptosis of neural cells and surrounding tissue cells, thus providing trophic support and improving regeneration conditions. It is highly likely that NGF and BDNF prevent neuronal death, with other factors present in PRP and PRF providing trophic support no neurons.

Osturk and colleagues (2018) [33] demonstrated that EGF regulates posttraumatic neural cell apoptosis. EGF treatment significantly decreased Bax and increased Bcl-2 protein expressions both in the spinal cord and the brain. Moreover, activities of antioxidant enzymes including catalase, superoxide dismutase and glutathione peroxidase were increased following EGF treatment [33]. Both PRP and PRF contain IGF-1 which promotes retinal progenitor cell proliferation via IGF-1 receptors, stimulating increased phosphorylation in the antiapoptotic metabolic pathways PI3K/Akt and MAPK/Erk [34, 35]. PDGF та IGF-1 exert neuroptotective effects after trauma through the stimulation of the neuroplastic potential and improvement in neurogenesis [12, 34-36].

Additionally, VEGF in PRP and PRF exerts an angiogenic effect, which is especially important when the lesion is ischemic in nature [5, 11].

Numerous studies have confirmed the anti-inflammatory effect of PRP and PRF due to the presence of transforming growth factor TGFβ that inhibits the activity of the transcription factor NF-kB at the site of injury [35, 38-40]. No doubt, a reduction in tissue edema is beneficial for improved trophic support for regeneration.

Therefore, the use of PRP and cell-free and stem-cell rich and progenitor-cell rich PRP matrices promotes neural cell and tissue recovery. This feature may be used to promote the regeneration of any peripheral nerve. In recent years, there have been reports on the results of the use of these autologous materials for visual function improvement.

In a study by Khan and colleagues [41], 0.2 mL of autologous PRP was injected in suprachoroidal space and 0.5 mL of PRP was injected in subtenon space of the intervention eye taking aseptic precautions. Injections were repeated at 15 day intervals up to 3 injections. Intervention eyes showed a statistically significant improvement in visual acuity and multifocal electroretinography (mfERG). Improvement was noted in amplitude density latency and in ring ratio of mfERG. There was a significant improvement in best-corrected visual acuity (BCVA) [41].

Todorich and colleagues [42] demonstrated that PRP can augment anatomical and visual outcomes in surgical repair of optic pit maculopathy. The patient had previously undergone vitrectomy and peripapillary laser, but had recurrence of subretinal fluid (SRF) and worsening visual acuity. PRP was layered over the pit and long-acting gas tamponade was performed with face-down positioning. This combination of surgical intervention with plasma therapy was found to be successful. At 8 months of follow-up, the patient's vision improved significantly from 20/100 to 20/50 [42].

Plasma products can also be used in the treatment of diabetic microangiopathy, a wide-spread disorder which is accompanied by retinal capillary changes and loss of pericytes. Dosso and colleagues [43] studied the effects of human blood derivatives and of a panel of individual growth factors on [3H]thymidine incopporation in bovine retinal pericytes and endothelial cells. Human serum and PRP stimulated incorporation of the nucleotide in a dose-dependent manner in both cell types. Consistent and

significant stimulation of DNA synthesis was observed, indicating high pericyte mitogenic activity of platelets. Thus, capillary regeneration and improvement in the blood supply to ocular tissues (including the retinal tissue) take place. Dosso and colleagues [43] believe that FGF-a, FGF-b and IGF-1 (the factors present in PRP) play a key role in this process.

Most recent advances in PRP research have been associated with plasma rich in growth factor (PRGF) [44]. In an experimental study, PRGF reduced blue-light induced oxidative damage to retinal pigment epithelial cells. Reactive oxygen species (ROS) synthesis was significantly reduced in PRGF-treated cells with respect to control. PRGF treatment preserved the mitochondrial activity and cell viability of RPE cells subjected to an oxidative stress, reduced the levels of oxidative stress and apoptotic enzymes and increased the expression of VEGF, the factor that contributes to vessel recovery [44].

Therefore, the use of PRP and PRGF in retinal cell lesions of various origins contributes to the preservation of cell viability, reduction of toxic exposure, and improvement in blood supply due to vessel recovery, which taken together leads to the recovery of (or improvement in) vision, with the exception of the cases with irreversible damage.

Given the above, it seems promising to use the PRP fibrin matrix that represents a 3D fibrin scaffold rich in plasma trophic factors. The matrix can be secured at the site of lesion in order to have a long-acting effect on the damaged tissue. In this way, Arias and colleagues (2022) [45] achieved complete macular hole closure in two patients, with the macular holes remaining close for 12 months at least. The extensive therapeutic potential of fibrin matrix includes the ability to provide not only anatomical, but also functional recovery of the retinal tissue through the stimulation of regenerative processes.

PRF has another advantage compared to other matrices: in addition to performing a scaffold function, it can serve as a media for the immobilization and trophic support of stem cells and progenitor cells. This significantly increases capabilities for the reparative effect. The 3D structure, the presence of pores, and amino-acid components make PRF a favorable environment for vital activities of cells [46]. Incorporation of a cell population into the fibrin matrix allows immobilizing it, which is very important for securing it at the site of lesion.

Bone marrow and adipose tissue mesenchymal stem cells (MSC) represent an autologous cell material that seems promising for neural repair. The capability of bone marrow MSC for neural repair is determined by their ability for neurologic differentiation and synthesis of neurotrophic factors [17-20, 46]. The capability of adipose tissue MSC for neural repair is determined by their ability for differentiation into Schwann cell and expression of BDNF and glial derived neurotrophic factor (GDNF) [21-23, 46].

The use of bone marrow and adipose tissue MSC has been found to be beneficial in the treatment of retinal degenerative disorders like age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy and glaucoma [47]. Holan and colleagues [47] believe that MSC replacement therapy (implemented through the neurogenic differentiation of MSC), and antiapoptotic and anti-inflammatory effects of the synthesis of biologically active substances by these cells are the major contributors to the efficacy of the use of autologous MSC in the above disorders. Taken together, the above factors lead not only to supporting the vitality of retinal cells and improving the retinal blood supply, but also to the potential formation of new cells to replace the lost ones [47].

A retrospective clinical study by Limpoli and colleagues [48] investigated the visual function changes in patients with glaucomatous optic neuropathy (GON) treated with the suprachoroidal MSC autograft by the Limoli retinal restoration technique (LRRT). At 6 months, the BCVA, close-up visus, and microperimetric sensitivity significantly improved in the LRRT-treated group ($p<0.05$) compared to controls. Limpoli and colleagues [48] believe that the suprachoroidal MSC autograft by the LRRT has proven to achieve retinal neural enhancement by producing growth factors directly into the choroidal space.

The use of stem cells in the treatment of age-related vision loss seems to be promising. Weiss and colleagues [49] demonstrated a successful application of autologous bone marrow-derived stem cells (BMSC) in the treatment of NAION. The average age of patients treated was 69.8 years. Affected eyes were treated with either retrobulbar, subtenons and intravenous BMSC or, following vitrectomy, intraoptic nerve, subtenons and intravenous BMSC. Following this therapy, 80% of patients experienced improvement in Snellen binocular vision ($P=0.029$) with 20% remaining stable. Improvements typically manifested no later than 6 months post-procedure. Weiss and colleagues [49] concluded that possible mechanisms by which visual improvement occurred include BMSC paracrine secretion of proteins and hormones, transfer of mitochondria, release of messenger RNA or other compounds via exosomes or microvessels and neuronal transdifferentiation of the stem cells.

Stem Cells Ophthalmology Treatment Study (SCOTS)-1 and SCOTS-2 are Institutional Review Board approved clinical studies utilizing autologous BMSC in the treatment of optic nerve and retinal diseases that meet inclusion criteria [49].

Therefore, it has been demonstrated experimentally and clinically that the use of stem and progenitor cells incorporated into the biomatrix significantly expands it regenerative potential due to the active viability of the stem cells secured at the site of lesion. The use of PRP-based stem- and progenitor cell-rich biological matrices rich provides the following effects:

- Inflammation relief due to immunomodulatory substances

- Release of growth and neurotrophic factors
- Improvement in the blood supply to the site of lesion due to revascularization of the damaged area
- Antiapoptotic effects
- Reduction in the sensitivity to oxidative stress due to activation of antioxidative enzymes, and
- MSC replacement therapy due to MSC differentiation.

Conclusion

The experimental and clinical data presented above indicate that PRP-derived autologous materials, when used in retinal neuronal and optic nerve lesions of various origins, stimulate regenerative processes, with the preservation of neural cell viability, resistance to toxic exposure, and improvement in vascularization.

The use of stem and progenitor cells incorporated into the matrix significantly expands it repair potential due to the direct differentiation of these cells, replacement of damaged and lost cells and release of a variety of biologically active substances directly at the site of lesion.

It is noteworthy that the use of autologous materials in eye disease treatment removes the risks associated with biological safety, potential immunological conflict, and late consequences of uncontrolled biological degradation.

Although the above clinical data undoubtedly indicate the beneficial effect of these materials, the data are diverse with respect to the diagnosis, patient age, severity of lesions, etc., and have not yet been transformed into a uniform system.

Therefore, there is a need for further clinical studies in this field, and accumulation and analysis of the data on the efficacy of the use of autologous biological materials in particular cases, to develop treatment protocols for particular diagnoses.

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Corresponding author: *Nataliia P. Oleksenko – N.oleksenko@gmail.com*

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Abbreviations: *: ADSC, adipose derived stem cells; BCVA, best corrected visual acuity; BDNF, brain derived neurotrophic factor; BMSC, bone marrow stem cells; EGF, epidermal growth factor; FGF, fibroblast growth factor; GDNF, glial derived neurotrophic factor; IGF-1, insulin-like growth factor 1; LRRT, Limoli retinal restoration technique; MSC, mesenchymal stem cells; NGF, nerve growth factor; PDGF, platelet derived growth factor; PRF, platelet rich fibrin; PRP, platelet rich plasma; TGFβ, transforming growth factor β; VEGF, vascular endothelial growth factor.*