Invited lecture/Scientific contribution/Original research

Facial Nerve Reconstructive Surgery in Otorhinolaryngology and its Enhancement by Platelet- and Extracellular Vesicle-Rich Plasma Therapy

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Abstract: The facial nerve and its reconstructive surgical procedures are complex and challenging. The main function of facial nerve is namely motor innervation of facial muscles and its dysfunction presents as facial paralysis. Depending on the extent of facial nerve injury (neurapraxia, axonotmesis, neurotmesis) and consequently a physiological phenomenon of Wallerian degeneration, mechanism, location of the injury, time course of the paralysis and medical condition we decide about the type of the reconstructive surgery. Generally, possible surgical interventions to improve facial nerve functioning are mainly nerve decompression, neurorrhaphy/end-to-end anastomosis, interposition (cable) grafts and nerve rerouting. Moreover, most commonly nerves undergoing facial reconstruction are great auricular and sural nerves. In addition, nerve rehabilitation can be improved by using platelet-rich plasma (PRP/PVRP), applied directly to nerve. There are many roles of PVRP, described in the literature such as neuroprotective, neurogenic, neuroinflammatory, angiogenic role and improving hemostasis. Also, its neoplastic and proliferative effects were not reported. Considering all these features implementing PVRP in the facial nerve regenerative treatment has strong potential in the future.

Keywords: Facial nerve; Reeconstructive surgery; Platelet and extracellular vesicle rich plasma; Nerve regeneration

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1. Introduction

The facial nerve or seventh cranial nerve is special among twelve cranial nerves due to its predominant motor innervation, multiple functions, varied composition and long and variable pathway (Battelino, 2013; Seneviratne et al., 2022). The article aims to focus on facial nerve reconstructive procedures and options to reestablish nerve integrity. The outcome of surgical procedures can be improved by using platelet rich plasma in surgical field (Vozel et al., 2020). Therefore, the article also covers the therapeutic effect of PRP/PVRP on facial nerve through the clinical case.

2. Facial nerve segments, its fiber components and nerve injury types

The facial nerve emerges from the facial nerve nuclei in the brainstem, where the *intracranial/ cisternal* pathway begins. After emerging the pons, nerve continues the *intrameatal/ canalicular* pathway along the internal auditory canal (IAC) with the vestibulocochlear nerve to the fundus and leaves it through the meatal foramen. The bony canal of facial nerve from IAC to the stylomastoid foramen is called the Fallopian canal where the facial nerve is often compressed due to inflammations. There are three segments of the Fallopian canal, a labyrinthine, a horizontal tympanic and a vertical mastoid segment. At the stylomastoid foramen the facial nerve leaves the temporal bone and branches at the pes anserinus into temporal, zygomatic, buccal, marginal and cervical branch. All muscles of facial expression are innervated by general somatic efferent fibers of facial nerve as one of five fiber types (Seneviratne et al., 2022; Toulgoat et al., 2013; Cummings, 2005; Probst et al., 2006). Facial nerve also receives taste sensations from anterior two-thirds of the ipsilateral side of the tongue and the palatal mucosa from afferent gustatory fibers. Furthermore, it carries parasympathetic secretomotor fibers to the submandibular, sublingual salivary glands, to the lacrimal glands and to the glands in the oral cavity. Postauricular skin, auricular concha and wall of the external auditory canal are supplied by somatosensory afferent fibers and nasal and pharyngeal mucosa by visceral afferent fibers of the facial nerve (Battelino, 2013; Takezawa et al., 2018; Phillips et al., 2018).

In general, to understand the mechanisms of facial nerve injuries, it should e acknowledged rgat every nerve fiber consists of endoneurium, surrounding each nerve fiber and attaches to the Schwann cell layer. It is important for endoneural tube regeneration and has poorer prognosis for regeneration when the layer is disrupted. Perineurium protects from spreading the infection and epineurium (nerve sheat) contains the vasa nervorum for nutrition (Pasha et al., 2014).

Depending on nerve injury cause (head trauma; parotid tumor compression; head and neck cancers; infectious diseases; peripheral nerve demyelinating lesions, etc.) we differentiate following types of nerve injury: Nneuropraxia –presents compression of the nerve, causing loss of axoplasmic flow without axonal rupture, due to focal segmental demyelination. The conduction block is most often resolved with complete recovery. Axonotmesis represents damaged axon with intact endoneurium where Wallerian degeneration occurs distal to site of injury, but complete recovery is anticipated. In neurotmesis, neural tube is transected; myelin sheath, axon, endoneurium, perineurium and epineurium are disrupted. Without surgical treatment there is no possibility to restore nerve function (Seddon, 1943; Bhandari, 2019).

3. Facial nerve reconstructive surgery – general

Almost every disruption of the continuity of the facial nerve should be fixed regardless of the cause being traumatic, iatrogenic injury or tumor invasion (Cummings, 2005). Interventions are limited to restoring the function of the motor fibers of the facial nerve and not of the remaining four types of facial nerve fibers (Chu et al., 2008). We roughly distinguish three types of reconstructive procedures in case of facial paralysis: facial nerve procedures, procedures involving other tissues at the affected facial side and procedures at the opposite, healthy facial side (Battelino, 2013). A general rehabilitation for facial nerve repair covers: spontaneous facial nerve repairment after observation; facial nerve neurorrhaphy (represents surgical suturing of divided nerve); facial nerve cable graft; nerve transposition; muscle transposition; microneurovascular transfer; static procedures (Cummings, 2005).
According to different facial nerve damage mechanisms and distinct involved pathways we distinguish between different reconstructive methods.

3.1. Facial nerve injury in temporal bone

In case of sudden facial paralysis, after imaging, we can make decompression of facial nerve which means relaxation of the facial nerve along the internal auditory canal and is possible in the first three extracranial segments (labyrinthine, tympanic and mastoid). The authors differentiate transmastoid (translabyrinthine) approach and middle fossa approach to decompress the nerve (Battelino, 2013; Cummings, 2005; Mehta, 2009). Retrolabyrinthine and retrosigmoid approaches can be used for intracranial segment of the facial nerve while preserving hearing (Cummings, 2005). The most demanding intervention of the facial nerve decompression is the area of the meatal foramen bony canal. Also transversely passing solid connective fibers compress the nerve (House et al., 1985; Fisch, 1974, Pulec, 1974; Darrouzet et al., 2001).
If facial nerve is transected, non-functioning facial nerve part should be removed and reconstructed by end-to-end anastomosis or by re-routing the nerve (Battelino, 2010) as described below.

3.2. Reconstruction of facial nerve in cerebellopontine angle (CPA)

Procedures in CPA with tumor that affects facial nerve functioning present a challenge. It is the goal of the surgery to ensure the stability of nerve stumps with sutures, thus using muscular fascia around them to achieve stability of necessary dendrites regrowth (Battelino et al., 2010). Approximation of the nerve ends using an acrylic glue has been described, and subsequent investigators have revealed that neural anastomosis with tissue adhesive yields results similar to nerve suture (Cummings, 2005; Ramos et al., 2015). Nevertheless, the literature reports about 21% to 35% failure rate of facial repair after reconstruction (Barfs et al., 1984; Pluchino et al., 1986). Using translabyrinthine approach accessed to the distal end of the facial nerve in the petrous bone, King et al. (1990) performed tha nerve repair by end-to-end anastomosis. Also, nerve was repaired by a graft, using the sutured great auricular nerve or by making faciohypoglossal nerve anastomosis (King et al., 1990). Arriaga et al. (1992) described direct facial nerve neurorrhaphy or anastomosis with a greater auricular nerve interposition graft as a successful repair option in cases after nerve transection in the CPA.

At the Department of Otorhinolaryngology and Cervicofacial Surgery professor Battelino and her team made end-to-end anastomosis of the facial nerve after middle fossa approach very close to pons where the lesion entered the IAC and destructed few millimeters of facial nerve. After removing the lesion, rerouting of the facial nerve and making facial nerve end-to-end anastomosis in IAC reconstructive procedures resulted in almost total facial expression symmetry at the rest.

3.3. Reconstruction in temporal segments

Reconstruction of transected facial nerve in facial bony canal presents three options: neurorrhaphy, interposition grafts and rerouting of facial nerve. Neurorrhaphy/ end-to-end anastomosis provides a tension-free anastomosis but is rarely used in practice (Mehta, 2009). End-to-side neurorrhaphy is used as an alternative technique when the proximal stump of an injured nerve is unavailable or the nerve gap is too long to be bridged by a nerve graft (Lykissas, 2011). Interposition (cable) grafts are used when a tension-free primary nerve repair is not possible (Mehta, 2009). Option for graft source are: the great auricular, sural nerve, the medial lateral antebrachial cutaneous nerves or ansa cervicalis. Overall, motor nerve grafts were indcated to be better than sensory nerve grafts (Chu et al., 2008). Grafts allow reparation of the facial nerve with minimal nerve end handling, thus leading to lesser impact on nerve vascularization and preserving the anatomy of the middle ear. The disadvantages of grafting include the interposition of another nerve between the stumps of the facial nerve resulting in two junctions between the ends of the affected nerve and the graft, and loss or reduction at the donor site (Chu et al., 2008; Humprey et al., 2008). Thirdly, rerouting facial nerve approximates the stumps of the sectioned nerve. This is exclusively important for gaining nerve length. However, it is much more difficult to perform free of suturing (Battelino, 2013; Filho et al., 2013).

3.4.Reconstruction of injured facial nerve in extratemporal region

The main reconstructive procedure of facial nerve after leaving the temporal bone in stylomastoid foramen is primary neurorrhaphy. It presents the best (but rare) possibility to regain the facial nerve function in case of tension-free closure with intact motor end plates. After the exit from the stylomastoid foramen, anastomosis with distally disrupted hypoglossal nerve can be made considering different modifications (Hadlock et al., 2005). Also, free nerve grafts can be connected to healthy facial nerve of the opposite side. In this case, nerve transplant is called "cross over" or "transposition nerve crossover". Later on, it can be sutured with subsequent transplants of smaller muscle groups in place of atrophied facial muscles (House et al., 1985; Fisch, 1974; Stark, 1987; Bailey et al, 2001; Glasscock et al., 1979). In nerve transfer procedures a variety of donor nerves such as hypoglossal, spinal accessory, masseteric branch of the trigeminal nerve and motor branches of the cervical plexus can be used (Mehta, 2009).

4. Platelet- and extracellular vesicle-rich plasma (PVRP) therapy and its contribution to nerve repair

4.1. General

Blood plasma obtained in a specific procedure that yields a preparation rich with platelets is an autologous blood-derived product with immune, hemostatic and regenerative effects (Vozel et al., 2020; Wang et al., 2022; Brisson et al., 2017; Tao et al., 2017; Uršič et al., 2014). As it contains also extracellular vesicles, it is conveniently called platelet- and extracellular vesicle-rich plasma (PVRP) (Vozel et al., 2020; , Alves et al., 2018). PVRP is prepared according to a simple and low cost procedure and can be applied in different fields of medicine (Vozel et al., 2020). After fixing nerve injury, regeneration by itself is slow and unpredictable (Fowler et al., 2015). It depends on the state of the destructed surrounding soft tissue and its blood supply (Wang et al., 2022). The number of studies on PVRP application for treatment of peripheral nerve injury has increased in the past decade and most of the studies have revealed that patients with peripheral nerve injury receiving PVRP treatment have an accelerated recovery (Wang et al., 2022). According to animal studies many molecules, released from platelet derived extracellular vesicles (PDEV) in PRP and after platelet stimulation, are responsible for nerve and other tissue regeneration and responses (Wang et al., 2022; Guo et al., 2017; Koupenova et al., 2018).

4.2. PVRP preparation and composition

PVRP with or without buffy coat can be prepared from blood by centrifugation (Božič et al., 2021). After sedimentation of erythrocytes that form about 45% of the blood volume (hematocrit), the remaining 54% yellowish supernatant presents plasma. A thin whitish layer between the two (of about 1 % of the blood volume) is called "buffy coat" and consists mostly of leukocytes and platelets (Vozel et al., 2020).
PVRP preparation can be delivered to target tissue as a liquid or a gel. It was indicated that PVRP gel is favorable for Schwann cells (SCs) and can effectively promote nerve regeneration (Ye et al., 2012). SCs are responsible for nerve cell proliferation and formation of migration bridges to the nerve stump (Wang et al., 2022). PVRP contains various growth factors (for example platelet-derived growth factor - PDGF, transforming growth factor β -TGF β, vascular endothelial growth factor - VEGF, epidermal growth factor - EGF and insulin-like growth factor - IGF-1, special peptides, immune system messengers, enzyme inhibitors and other bioactive compounds (Arslan et al., 2022).

4.3. PVRP's potential of nerve repair and its enhancement

Nerve regeneration depends on lifetime, gender, patient's health condition, and associated diseases (Kuffler et al., 2020). Listed factors can be bypassed and the treatment improved with PVRP since it has neuroprotective, neurogenic and neuroinflammatory modulatory effects (Sánchez et al., 2018). Sánchez et al. (2018) described six levels of PVRP's potentials to promote nerve regeneration with biomolecules and different growth factors that act neuroprotectively: prevention of neuronal apoptosis; stimulation of vascular regeneration; promotion of axonal

regeneration; regulation of inflammatory response in the microenvironment; alleviation of nerve collateral muscle atrophy; improvement of human nervous system parameters (Sánchez et al., 2018). Moreover, Arslan et al. (2022) pointed to angiogenic role of PVRP and observed no neoplastic or proliferative effects of PVRP (Arslan et al., 2022).

Nerve injury closer to the cell body causes neuron death, therefore nerve fibers distally from the cell body start regenerating. The debris of nerve tissue is destroyed by macrophages recruited from peripheral blood or nerve tissue, which can provide a suitable environment for nerve regeneration. We know that released growth factors are mostly responsible for SCs proliferation, its migration and promotion of axon regeneration. Li et al. (2017) described PVRP's positive effects on facial nerve trauma by improving Schwann cell and axon recovery (Li et al., 2017). Moreover, platelet-derived growth factor-BB (PDGF-BB) and IGF-1 may be the main cytokines affecting SC proliferation and migration. Vascular endothelium growth factor (VEGF) as a powerful angiogenic factor, released by macrophages, that is specific to the vascular endothelium, was shown to have chemotaxis effects, to promote axonal growth and neuronal survival (Wang et al., 2022). Also, its neuroprotective role was indicated due to positive effects on motor neuron survival and reduction of ischemic conditions (Hillenbrand et al., 2015). Pelletier et al. (2015), found that application of VEGF gene therapy to nerve regeneration resulted in positive correlation between increased vascularization and enhanced nerve regeneration. Therefore, VEGF application may play a role in promoting the growth of degenerated nerve fibers through the combined effects of angiogenesis, neurotrophy and neuroprotection (Pereira Lopes et al., 2011).

Protein 1 from Schwann cells promotes migration and recruitment of macrophages that manage regeneration. Injured axons release neuropeptides - substance P and calcitonin-gene-related peptide to cause neurovascular dilatation (Wang et al., 2022; Arslan et al., 2022).

Peripheral nerve injury repair involves various inflammatory cells, including macrophages which destroy debris of nerve tissue. Macrophages fall into two phenotypes-the classical activated macrophage M1 and selectively activated macrophage M2 (Delavary et al., 2011). In hypoxic condition, macrophages adapt to the microenvironment by secreting VEGF-A, which stimulates blood vessel formation in the direction of nerve regeneration. Schwann cells do not secrete high levels of macrophages M2, but act as inducers for promoting axonal outgrowth (Stratton et al., 2018).

In otorhinolaryngology, Ricci et al. (2019) have analyzed the efficiency of PVRP gel in superficial parotidectomy for benign tumors, applying it on the remaining parotid gland and the branches of the facial nerve. Their study revealed a positive effect of PVRP gel on clinical outcomes, postoperative observed facial palsies were reduced (Ricci et al., 2019). Scala et al. (2014) after using PVRP gel on patients who underwent superficial parotidectomy found a positive trend in the PVRP-group regarding facial nerve impairment (Scala et al., 2014).

4.4. Use of PVRP plasma in clinical practice regarding facial nerve

A 83-years old male patient with recidivant and advanced invasive squamous carcinoma of ear, external auditory canal and neck and parotid metastasis was planned for extensive surgical procedure to remove carcinoma (**Figure 1**). Because of endangered facial nerve it was controlled by neuromonitoring. After tumor excision and subtotal petrosectomy, facial nerve was preserved and PVRP gel was applied directly to the facial nerve. In our case and in general, PVRP gel application is important after relaxation of facial nerve from stylomastoid foramen as well as in case of compromised arterial supply, since PVRP induces neoangiogenesis. Immediately after the procedure, facial nerve was slightly affected due to tension of tissue removal manipulation, but at the later check-ups its facial motor skills were normalized.

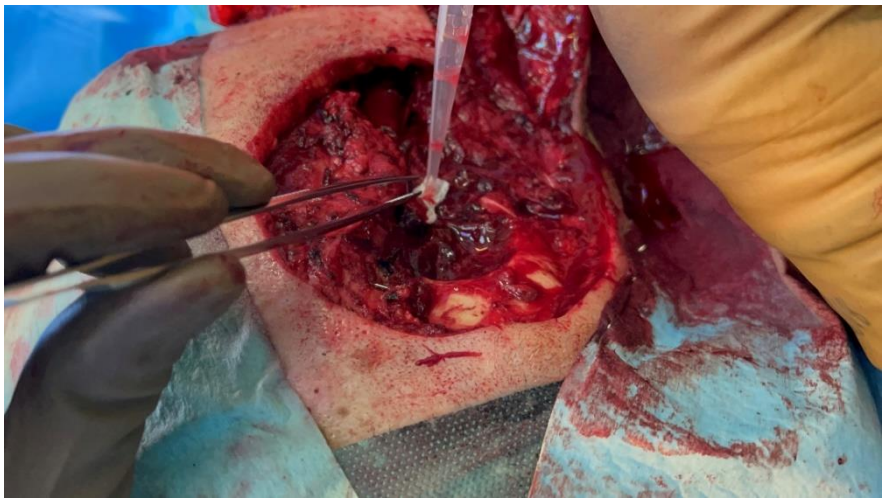

Figure 1. Applying PVRP gel directly to facial nerve.

5. Conclusion

Facial nerve injury has strong negative impact on patient 's health and quality of life. Surgical interventions and management of facial nerve reconstructions are complex. Reconstructive and nerve repairing outcomes can be improved by using PVRP which has proved safe due to local applications and no observed side effects. We anticipate that wide using PVRP in nerve repair procedures will bring revolution in patients' nerve rehabilitation due to already indicated hemostatic, neuroprotective, neurogenic, neuroinflammatory and angiogenic effects and no record of neoplastic or proliferative effects.

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