Review

Advancements of Platelet-Rich Products and Extracellular Vesicle Use in Otology

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Abstract:
Autologous blood-derived platelet-rich products exert their regenerative effects by modulating molecular processes involved in hemostasis, inflammation, angiogenesis, cellular transport, cytoskeleton synthesis and other. Abnormalities in these biological processes can be observed in many conditions, including otologic diseases. The action of bioactive components of extracellular vesicles and platelets in platelet-rich preparations presents an additional therapeutic possibility in managing several otologic pathologies, especially where other interventions for enhancing wound healing, tissue regeneration, and reducing inflammation have been exhausted. The application of platelet-rich preparations has been explored in chronic middle ear disease, tympanic membrane perforation, sudden hearing loss, facial nerve damage and other. Furthermore, extracellular vesicles, which are present in all bodily fluids including platelet-rich preparations, have been increasingly investigated as a potential diagnostic and target therapeutic tool in the management of hearing loss.

Keywords: Platelet-rich Plasma; Extracellular vesicles; Otology; Growth Factors; Hearing Loss

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1. Introduction

By providing small particles to tissues and aiding in establishing an optimal molecular microenvironment for tissue regeneration, platelet-rich products have been utilized across various fields of medicine yielding favourable results (Troha et al.,2023). Otology, a subspecialty focused on the diagnosis and treatment of ear-related disorders, is no exception in the attempts of exploring the beneficial effects of these products.

Platelet rich products are most commonly described in the literature as platelet-rich plasma (PRP) or platelet and extracellular vesicle-rich plasma (PVRP), the latter emphasizing the importance of extracellular vesicles (EVs) in these fluids. PRP and PVRP are autologous blood-derived products with platelet concentrations 3-5 times higher than whole blood (Marx et al.,2001; Tao et al., 2017). EVs are a heterogeneous group of cell-derived membranous structures, harvested from any bodily fluid, including PRP and PVRP. Depending on their origin, EVs play a role in physiological and pathological processes and can be categorized endosome-origin exosomes and plasma-derived ectosomes (further divided into microvesicles, microparticles, ectosomes, large oncosomes and apoptotic bodies). These nano- and microvesicles are especially recognized for their involvement in membrane and cytosol transport, as well as RNA delivery, the mechanisms by which EVs are being investigated for their potential use in the diagnosis and treatment of a range of diseases (Tao et al., 2017; Dai et al., 2020; Raposo et al., 2013; Steiner & Battelino, 2020; Sluga et al., 2021). In addition to EVs, platelets have been identified as the central mediators of beneficial effects of platelet-rich preparations, participating in essential processes of hemostasis, inflammation, angiogenesis, tissue anabolism, extracellular matrix synthesis, as well as in immune system modulation (Morrell et al., 2014; Anitua et al., 2004) . The main bioactive molecules promoting healing in platelet-rich preparations include growth factors, cytokines and other compounds (Anitua et al., 2004; Sundman et al., 2011). The preparation of platelet-rich products is cost-beneficial, straight-forward and involves simple centrifugation, performed either in one or two steps. After centrifugation, platelets in the preparation can be activated either exogenously (using chemical substances like calcium chloride) or endogenously (in vivo after application). A significant advantage of exogenous application is the formation of a gel-like consistency, which facilitates application onto tissues. However, its application should occur within 10 min after activation, in the time frame where most of the beneficial constituents are released (Marx et al.,2001; Croisé et al., 2020; Božič et al., 2021). Platelet-rich products have been found as inherently safe to use in tissues, acting similarly to a blood clot (Andia et al., 2013). Studies investigating possible oncogenic effects (Marx et al.,2001; Marx et al; 1998), or long-term use in animal models (Omar et al., 2017), as well as in sensitive tissues, such as in the middle ear (Arslan et al., 2022) have shown no adverse effects. Instead, the investigations demonstrated significant anti-inflammatory and regenerative potential (Arslan et al., 2022). In addition, it has been shown that the preparations can be tailored in their composition to optimize its therapeutic effect depending on the clinical context, especially regarding the presence or absence of the inflammation process, and on the patients' own blood characteristics (Sundman et al., 2011; Steiner et al., 2022).

2. Application of PRP/ PVRP in otology

Studies investigating the tissue regeneration and anti-inflammation functions have made platelet-rich preparations a promising adjunctive treatment modality in otologic diseases, such as middle ear diseases (e.g., tympanic membrane perforation, chronic otitis media), nerve preservation (sudden sensorineural hearing loss, chorda tympani nerve manipulation, facial nerve injuries) and other (Sherif et al., 2024; Mandour et al., 2019; Lee et al., 2017). Some examples and findings of clinical studies are presented in the **Table 1**.

Table 1. Examples of studies with PRP/PVRP application in otology. PRP; platelet-rich plasma, PVRP; platelet and vesicle-rich plasma.

Authors and year of publication, type of study and number of subjects	Use in otology	Results
Shiomi and Shiomi (2020): retrospective study, 118 patients; Fouad et al. (2018) : retrospective study conducted, 69 patients; El-Anwar et al. (2015) randomized controlled trial, 64 patients; Mandour et al. (2019) : prospective randomized controlled study, 50 patients; Huang et al. (2021), meta-analysis, 8 studies; Al-Arman et al. (2024) : randomized clinical trial, 156 patients.	Tympanic membrane perforation – use in myringoplasty	• Significantly improves healing of perforations, also suitable for larger perforations.
Kanauija et al. (2023): prospective interventional study, 70 patients; Dave et al. (2021) : case series, 40 patients; Tom et al. (2022): prospective observational study, 54 patients; Tyagi & Rout (2019): Case series study, 200 patients; Arslan et al. (2022) : experimental animal study.	Sudden sensoryneural hearing loss	• Substantially improves hearing in acute hearing loss. • One-time intratympanic injection yields better results compared to intratympanic steroids, no complications. • Favourable results in younger patients. • Proven safe use in the middle ear.
Askar et al. (2021): case series, 21 patients. Jang et al. (2016): experimental animal study.	Mastoid reconstruction after CWD (canal wall-down) mastoidectomy .	• Good healing and epithelization of radical cavity. • Better visualisation upon follow-up imaging as in obliteration with other materials.
Vozel et al. (2021) [30]: randomized controlled trial, 22 patients.	Chronic discharging radical cavity	• Successful outcomes in cases of standard therapy failure.
Lee et al. (2017): case study, 1 patient.	Pinna replantation site	• Supports neovascularization and transplant protection after reperfusion ischemia.

2.1. *Tympanic membrane perforation*

Acute and chronic tympanic membrane perforations in acute or chronic form, traumatic or as a consequence of chronic otitis media present a common otologic disease often requiring a surgical intervention. Tympanoplasty is a surgical procedure with reported success rates from 75% to 98% (Mohamad et al., 2012; Sheehy et al.,1980), but tends to be less effective in patients with larger perforations, in those with early onset of middle ear discharge postoperatively, and in patients with myringosclerosis. Especially in cases of recurrent perforations, additional support (such as cartilage graft) is usually provided to the most commonly used temporalis fascia graft. As a means of enhanced aid to graft incorporation and therefore in promoting the closure of the perforation several studies have demonstrated the beneficial effects of PRP and PVRP (Singh & Jain, 2024). Huang et al. (2021) performed a systematic review and meta-analysis, where the efficacy of PRP in myringoplasty was investigated. The analysis included eight studies involving 455 patients. The results showed a significant increase in the closure rate for PRP-treated patients compared to conventional surgery, indicating that PRP significantly enhances the healing process. Moreover, the use of PRP was associated with a lower incidence of complications. However, no significant differences in hearing in patients with closed tympanic membrane improvements between PRP and conventional methods were noted (Yadav et al., 2018). Yadav et al. (2018) demonstrated the use of PRP as applied in an underlay technique between temporalis fascia and tympanic membrane in a study of 20 patients, reporting a significant difference in graft uptake in favour of the PRP group compared to the control after 3 months (Yadav et al., 2018). Akash et al. (2023) conducted a RCT on 40 patients with the use of PRP as packing material in type 1 tympanoplasty in chronic otitis media and 40 in the control group, observing the status of graft uptake and reperforations at 1st and 6th month postoperatively. The results showed similar graft uptake and reperforations as well as the rate of post-operative infections in both groups (Akash et al. 2023). In a study by Yousaku Shiomi & Yoshiko Shiomi (2020), the researchers assessed the outcomes of myringoplasty using PRP and atelocollagen sponge foams and found that PRP significantly improved the rates of closure, especially for small perforations. The cause and duration of perforation were not predictors of the outcome, while the patient age was significantly correlated to the surgical success. Subjects older than 80 years had a significantly lower success rate than younger patients (Yousaku Shiomi & Yoshiko Shiomi, 2020). Fouad et al. (2018) compared the outcomes of fat graft myringoplasty (FGM) with PRP or with hyaluronic acid (HA) versus to FGM alone in patients with medium-sized perforations. They reported a significantly higher success rate (85.7%) in patients with PRP than those with FGM alone (60%) (Fouad et al. ,2018). El-Anwar et al. (2015) supported the favourable results of PRP use by reporting a 100% success rate in myringoplasty with conchal perichondrial graft with PRP in 32 patients, compared to 32 patients without PRP, all with large dry central perforations. 81.25% success rate was reported in the control group. Additionally, in the test group, a reduced incidence of postoperative infections was noted (El-Anwar et al.,2015). Mandour et al. (2019) compared PRP-enriched fat grafts and reconstruction with cartilage perichondrium in 50 patients undergoing myringoplasty and demonstrated that both approaches yielded comparable results, with an 88% closure rate in the PRP-fat graft group and 92% in the cartilage group. The researchers concluded that PRP addition in fat-graft myringoplasty can be recommended as first line treatment of medium-size central perforations of the tympanic membrane. They additionally proposed that the preparations are effective in transplant durability by preventing dehydration at the margins of tympanic membrane perforations (Mandour et al.,2019). Choudhury et al. (2024) investigated the use of fat grafts combined with PRP in small and moderate perforations in 36 patients and reported a high success rate, suggesting that the convention of using the temporalis fascia graft for smaller perforations should be revisited (Choudhury et al. 2024). Similarly, Al-Arman et al. (2024) compared the efficacy of platelet-rich fibrin-augumented fascia to established cartilage tympanoplasty for large perforations in a RCT study of 156 patients. Graft take and hearing outcomes showed no significant difference, with no complications reported, suggesting PRP as a comparable option without the need of cartilage harvest . Braccini et al. (2009) previously reported a success rate of 96% in tympanoplasty using leucocyte- and platelet-rich fibrin (L-PRF), compared to 85% successful outcomes in tympanoplasty without PRF. The researchers proposed that PRF provides both mechanical

and inflammatory protection to tympanic grafts (Braccini et al.,2009). Sankaranarayanan et al. (2013) found that the PVRP clot application during tympanoplasty prevented graft displacement, facilitating the closure of the perforation.

2.2. *Sudden sensorineural hearing loss and other nerve impairment in otology*

Sudden sensorineural hearing loss (SSHL) is an abrupt deterioration of hearing for at least 30 dB in 3 or more consequent frequencies upon audiometric evaluation, in the time period of 72 h. It is termed idiopathic when the etiology remains unclear after clinical (otologic and audiologic) examination and patient history. Researchers Ding et al. (2009) priorly suggested that the application of PRP has potential regenerative effect on cranial and peripheral nerves, which was later confirmed in different animal and clinical studies (Shen et al, 2019; Li et al., 2019; Kuffler et al., 2011). Sanchez et al. (2017) proposed that platelet-rich products influence nerve repair by mechanical protection, neuron apoptosis prevention, stimulation of angiogenesis, axon regeneration promotion and inflammation modulation in the microenvironment of nerve cells. Singh & Jain (2020) reviewed the role of platelet-rich product use in management of sensorineural hearing loss and concluded that may facilitate the repair and regeneration of damaged auditory cells and nerve fibers, potentially improving hearing function in individuals with SNHL. Arslan et al. (2022) also investigated in an animal model the effects of PRP application intratympanically and found no adverse effects, with lower degrees of inflammation and mucosal thickness versus the control side, and with more evident angiogenesis on the tested side. They suggested that PRP is a safe alternative to current treatment with its the anti-inflammatory and regenerative features. Mahmoud Shawky (2024) conducted a study, where intratympanic PRP injections were compared to steroid intratympanic injections in managing SSHL. A significant improvement in hearing after 2 weeks for 25 dB and after 2 months for 30 dB was observed in the PRP group. Tyagi & Rout. (2019) similarly previously reported patients with mild to moderate SNHL to recover significantly after intratympanic PRP injection, especially in younger patients. Stephy Maria Tom et al. (2022) reported 54 cases with sensory neural hearing loss treated with PRP or dexamethasone intratympanically. In the PRP group, improvement from baseline was significantly higher in PRP group compared to dexamethasone group. Kanauija et al. (2023) administered intratympanic PRP injections in 70 patients, where hearing loss was present for less than 6 months, of which 85.2 % recovered completely and 14.8% partially. Intratympanic PRP injection significantly improved hearing in acute mild-to-severe cases of sensory hearing loss with no complications reported. Sherif et al. (2024) conducted a comparative study of intratympanic steroid and PRP injection and found no significant differences in treatment modalities, both proving to be similarly effective in improving hearing outcomes in sudden sensorineural hearing loss. Additionally, PRP's neurotropic effects were investigated in cases of facial nerve dysfunction, whether after salivary gland or temporal bone surgery (Bitenc Zore et al., 2022). Ricci et al. (2019) and Scala et al. (2014) have shown that the application of PRP in gel form after superficial parotidectomy reduces the occurrence of postoperative facial palsy. In the study of Cho Hyong-Ho et al. (2010) PRP in combination with neural-induced mesenchymal stem cells was administered to the facial nerve in animal models, showing significant facial nerve regeneration. These effects were attributed to neurotrophic growth factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Moreover, with the idea to aid nerve regeneration and reduce postoperative sensory impairment, an unpublished study is currently underway evaluating the use of PVRP on the chorda tympani nerve, responsible for taste sensation in the anterior two-thirds of the tongue and is commonly stretched or damaged during middle ear surgeries, resulting in taste and other sensory disturbance in the tongue.

2.3. *Radical cavity reconstruction and chronic radical cavity inflammation*

In cases of chronic otitis media with cholesteatoma and subsequent need for surgery, often a radical cavity is formed, which is an operative hollowing of temporal bone performed in canal wall down mastoidectomy surgery. This postoperative cavity can be afflicted with complications such as chronic inflammation with discharge. A study by Elbary et al. (2018) demonstrated the benefits of combining titanium mesh and PRP with bone material in the reconstruction of the posterior meatal wall in middle ear cholesteatoma surgery. This

method was found to be reliable, without complications, giving a smooth appearance to the area and improving healing. In order to aid the epithelization of the radical cavity and reduce the inflammation, Askar et al. (2021) used PRP in addition to bone pate in mastoid reconstruction and demonstrated improved healing, reduction of incidence of complications and better visualization during follow-up imaging for recurrences. Similarly, Vozel et al. (2021) in randomized controlled trial described PVRP as an effective treatment modality for chronic postoperative temporal bone cavity inflammation. For obliterating surgical cavities, Zwierz et al. (2024) used injectable platelet-rich fibrin on a temporoparietal fascial flap in three cochlear implant patients after subtotal petrosectomy due to chronic discharging ears and concluded that this material may reduce the risk of potential infection in the obliterated cavity, in patients without cholesteatoma.

2.4. Ototoxicity

The protective effects of PRP against ototoxicity have also been documented. It was reported that intratympanic administration of PRP can mitigate the ototoxic effects of cisplatin in experimental models, alluding to the potential to preserve auditory function (Yurtsever et al., 2020). In fact, growth factors present in PRP, such as Insulin-like Growth Factor-1 (IGF-1) were suggested to play a role in protecting hair cells from ototoxic damage (Dave et al., 2021).

2.5. Other uses

Lee et al. (2017) described a case of a complete ear amputation in a patient, where PRP was injected along with hyperbaric oxygen therapy and polydeoxyribonucleotide, demonstrating facilitation of neovascularization and protection against transplant failure due to reperfusion ischemia with almost complete salvage of the pinna.

3. Advancements in treating sensorineural hearing loss: EVs and autologous platelet-rich preparations

Sensorineural hearing loss is a result of multiple causes, including genetic predisposition, infections, ototoxic agents, exposure to noise, aging. It presents a substantial clinical challenge with no effective pharmacological treatments, despite the high prevalence of the condition globally. As to act to prevent the loss of hair cells or auditory neurons, modern research focuses to protect and regenerate cochlear cells before cell loss. In efforts to establish restoration of cochlear synapses, neurotrophins such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) were proposed (Fritzsch et al., 2004). These regulate the connection between hair cells and auditory neurons during embryogenesis and stabilize the cochlear synapses (Bailey et al., 2014; Warnecke et al., 2020). It has been demonstrated that especially a various composition of neurotrophins has the ability to increase the survival of auditory neurons, compared to single factors alone. Treatment with EVs have been proposed as therapeutic agents, especially containing the mentioned neurotrophins, BDNF and NT-3. PRP and autologous mononuclear cells derived from human bone marrow have been investigated as sources of these factors, since a balanced combination of various factors are naturally occurring in these preparations (Schwieger et al., 2015; Kranz et al., 2014; Kaiser et al., 2013). In addition to a potential therapeutic role, Wong et al. (2018) reported that EVs from rats' primary cultured inner ear cells release exosomes, which could be used as a biomarker showing the state of the inner ear, as the change in EVs' cargo and concentration was noted by exposure to cisplatin or gentamycin. The authors also suggested the isolated EVs could be loaded with anti-inflammatory drugs, therefore, the vesicles could be used as nanocarriers. Zhuang et al. (2021) demonstrated EVs in human perilymph, which were carrying hair cell-specific proteins and suggested that sensory hair cells themselves were the potential source of exosomes. The isolated EVs had specific miRNA and protein cargo profile, derived from different developmental stages of the inner ear postnatally. The study also postulated that these EVs may reflect the physiological and pathophysiological processes in the inner ear (Jiang et al., 2022) . This was demonstrated further on examples of EVs from vestibular schwannoma (VS) cell culture. Exosomes from VS cell cultures were shown to likely damage hair cells and auditory neurons from patients with VS and poor hearing, than those of EVs from patients with VS and good hearing (Soares et al., 2016). Protective

functions of EVs have also been investigated such as in protection of hair cells against aminoglycoside toxicity, where researchers used utricle-derived exosomes (Breglio et al., 2020). Moreover, Warnecke and colleagues in 2020 showed that mesenchymal stem cell (MSC) EVs contain neurotrophic factors and that the application of these EVs to the cochlea protected auditory hair cells from noise-induced trauma in vivo. The same researchers first introduced in-human intracochlear application of allogeneic human stromal derived extracellular vesicles during cochlear implantation (Warnecke et al., 2020). Tsai et al. (2021) subsequently showed that the administration of umbilical cord-MSC-EVs to cochlear hair cells in mice after repetitive cisplatin injection improved hearing. et In addition, EVs have been investigated in neuro-otology as compounds of viral vector gene therapy, which was previously inefficient in the delivery of genes to all the hair cells of the inner ear. By a vector called exosome-associated adeno-associated-virus (exo-AAV), it was demonstrated that the genes were significantly delivered to all inner ear hair cells, inner and outer. It was shown that AAV with exosomes rescued hearing in a mouse with hereditary deafness (György et al., 2017).

3.1. Adverse effects of use in middle ear

As noted previously, the adverse effects of platelet-rich products are extremely rare, there are no concerns about transmittable disease, since the preparation is autologous. Studies have shown that the slightly acidic pH of PRP compared to a matured blood clot, PRP acts inhibitory to bacterial growth, which is beneficial in PRP applications. To assess the safety of the use in the middle ear Arslan et al. (2022) demonstrated a safe prolonged use on the middle ear mucosa, with degrees of inflammation and mucosal thickness significantly lower in middle ear treated with PRP compared to the control side treated with saline. In fact, favourably, the degree of angiogenesis was significantly higher in the PRP administered side, promoting regeneration.

4. Conclusions

Autologous platelet-rich blood-derived products are versatile and effective treatment options in otologic disease management with minimal adverse effects due to the autologous nature. The components of the preparations, released in a manner similar to blood clot formation, are involved in healing promotion, inflammation reduction, cell regeneration and angiogenesis. These effects are being used in treatment of sudden sensorineural hearing loss, tympanic membrane perforation, ototoxicity and others, making it a valuable adjunct in clinical otology practice. In recent time, it has additionally been shown that the natural composition of small particles called extracellular vesicles can be used as vectors for gene therapy in transport to all inner ear hair cells, which previously failed, potentially treating sensorineural hearing loss. In the future, personalized protocols with preparations adapted to the clinical case may be expected. Further combinations of platelet-rich products with other adjuvants, such as PRP with gene therapy, stem cells, biomaterials, may be developed in order to enhance the beneficial clinical outcomes. Further studies are needed to support the existing hypotheses.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Akash, Datta R, Suri GS, Mucha S, Sheikh MA, Taneja NS. A Randomised Controlled Trial on the Efficacy of Topical Application of Autologous Platelet Rich Plasma (PRP) on Graft Uptake Rate in Adults Undergoing Type 1 Tympanoplasty for Inactive COM Mucosal Disease. Indian J Otolaryngol Head Neck Surg. 2023; 75:605-613. DOI:10.1007/s12070-023-03681-w
2. Al-Arman AM, Moneir W, Amer HE, Ebada HA. Platelet rich fibrin augmented tympanoplasty versus cartilage tympanoplasty: a randomized clinical trial. Eur Arch Otorhinolaryngol. 2024; 281:5739-5746. DOI:10.1007/s00405-024-08819-2
3. Andia I, Abate M. Platelet-rich plasma: underlying biology and clinical correlates. Regen Med. 2013;8:645-658. DOI:10.2217/rme.13.59

4. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous Platelets as a Source of Proteins for Healing and Tissue Regeneration. Thromb Haemost 2004, 91:4–15. DOI:10.1160/TH03-07-0440.
5. Arslan N, Kargin Kaytez S, Ocal R, Yumusak N, Şenes M, Ibas M. Possible Neoplastic or Proliferative Effects of Intra-Tympanic Platelet-Rich Plasma on the MiddleEarMucosa: A Myth or a Fact to Consider?. J Int Adv Otol. 2022;18:252-256. DOI:10.5152/iao.2022.20116
6. Askar SM, Saber IM, Omar M. Mastoid Reconstruction With Platelet-Rich Plasma and Bone Pate After Canal Wall Down Mastoidectomy: A Preliminary Report. Ear Nose Throat J. 2021; 100:485-489. DOI:10.1177/0145561319879789
7. Bailey EM, Green SH. Postnatal expression of neurotrophic factors accessible to spiral ganglion neurons in the auditory system of adult hearing and deafened rats. J Neurosci. 2014; 34:13110-13126. DOI:10.1523/JNEUROSCI.1014-14.2014
8. Bitenc Zore S, Vozel D, Battelino S. Facial Nerve Reconstructive Surgery in Otorhinolaryngology and Its Enhancement by Platelet- and Extracellular Vesicle-Rich Plasma Therapy. In Proceedings of the Socratic Lectures 7; University of Lubljana Press, September 1 2022; pp. 29–36.
9. Božič D, Hočevar M, Kisovec M, Pajnič M, Pađen L, Jeran M, Bedina Zavec A, Podobnik M, Kogej K, Iglič A, et al. Stability of Erythrocyte-Derived Nanovesicles Assessed by Light Scattering and Electron Microscopy. Int J Mol Sci. 2021; 22:12772. https://doi.org/10.3390/ijms222312772
10. Braccini F, Tardivet L, Dohan Ehrenfest DM. Place des facteurs de croissance (Platelet-Rich Fibrin de Choukroun) dans la chirurgie de l'oreille moyenne: résultats préliminaires [The relevance of Choukroun's Platelet-Rich Fibrin (PRF) during middle ear surgery: preliminary results]. Rev Laryngol Otol Rhinol (Bord). 2009; 130:175-180.
11. Breglio AM, May LA, Barzik M, et al. Exosomes mediate sensory hair cell protection in the inner ear. J Clin Invest. 2020; 130:2657-2672. DOI:10.1172/JCI128867
12. Croisé B, Paré A, Joly A, Louisy A, Laure B, Goga D. Optimized centrifugation preparation of the platelet rich plasma: Literature review. J Stomatol Oral Maxillofac Surg. 2020; 121:150-154. DOI:10.1016/j.jormas.2019.07.001
13. Cho HH, Jang S, Lee SC, et al. Effect of neural-induced mesenchymal stem cells and platelet-rich plasma on facial nerve regeneration in an acute nerve injury model. Laryngoscope. 2010; 120:907-913. DOI:10.1002/lary.20860
14. Choudhury B, Gupta P, Mandal S, Sharma V, Soni K, Kaushal D. Platelet-Rich Plasma in Fat Graft Type-1 Tympanoplasty - Should We or Should We Not?. Int Arch Otorhinolaryngol. 2024; 28:e614-e618. DOI:10.1055/s-0044-1787169
15. Dai J, Su Y, Zhong S, et al. Exosomes: key players in cancer and potential therapeutic strategy. Signal Transduct Target Ther. 2020; 5:145. DOI:10.1038/s41392-020-00261-0
16. Dave VJ, Joshi A, Bradoo R, Prajapati M, Shah K. Effects of Insulin-Like Growth Factor (IGF-1) in Patients with Sensorineural Hearing Loss. J Int Adv Otol. 2021;17:207-214. DOI:10.5152/iao.2021.8549
17. Ding XG, Li SW, Zheng XM, Hu LQ, Hu WL, Luo Y. The effect of platelet-rich plasma on cavernous nerve regeneration in a rat model. Asian J Androl. 2009; 11:215-221. DOI:10.1038/aja.2008.37
18. El-Anwar MW, El-Ahl MA, Zidan AA, Yacoup MA. Topical use of autologous platelet rich plasma in myringoplasty. Auris Nasus Larynx. 2015; 42:365-368. DOI:10.1016/j.anl.2015.02.016
19. Elbary MEA, Nasr WF, Sorour SS. Platelet-Rich Plasma in Reconstruction of Posterior Meatal Wall after Canal Wall Down Mastoidectomy. Int Arch Otorhinolaryngol. 2018; 22:103-107. DOI:10.1055/s-0037-1602694
20. Fouad YA, Abdelhady M, El-Anwar M, Merwad E. Topical platelet rich plasma versus hyaluronic acid during fat graft myringoplasty. Am J Otolaryngol. 2018; 39:741-745. DOI:10.1016/j.amjoto.2018.08.004
21. Fritzsch B, Tessarollo L, Coppola E, Reichardt LF. Neurotrophins in the ear: their roles in sensory neuron survival and fiber guidance. Prog Brain Res. 2004; 146:265-278. DOI:10.1016/S0079-6123(03)46017-2
22. György B, Sage C, Indzhykulian AA, et al. Rescue of Hearing by Gene Delivery to Inner-Ear Hair Cells Using Exosome-Associated AAV. Mol Ther. 2017; 25:379-391. DOI:10.1016/j.ymthe.2016.12.010
23. Huang J, Shi Y, Wu L, Lv C, Hu Y, Shen Y. Comparative efficacy of platelet-rich plasma applied in myringoplasty: A systematic review and meta-analysis. PLoS One. 2021; 16:e0245968. DOI:10.1371/journal.pone.0245968
24. Jang CH, Choi CH, Cho YB. Effect of BMP2-Platelet-rich Plasma-Biphasic Calcium Phosphate Scaffold on Accelerated Osteogenesis in Mastoid Obliteration. In Vivo. 2016; 30:835-839.
25. Jiang P, Ma X, Han S, et al. Characterization of the microRNA transcriptomes and proteomics of cochlear tissue-derived small extracellular vesicles from mice of different ages after birth. Cell Mol Life Sci. 2022; 79:154. Published 2022 Feb 26. doi:10.1007/s00018-022-04164-x
26. Kaiser O, Paasche G, Stöver T, et al. TGF-beta superfamily member activin A acts with BDNF and erythropoietin to improve survival of spiral ganglion neurons in vitro. Neuropharmacology. 2013; 75:416-425. DOI:10.1016/j.neuropharm.2013.08.008

27. Kanaujia SK, Singh M, Gautam HK, Ruchika F, Purwar AK, Arya A, Singh S, Srivastava A. Role of Platelet-Rich Plasma in Sensory Neural Hearing Loss. An International Journal of Otorhinolaryngology Clinics 2023; 15:38–41. DOI:10.5005/jp-journals-10003-1438.
28. Kranz K, Warnecke A, Lenarz T, Durisin M, Scheper V. Phosphodiesterase type 4 inhibitor rolipram improves survival of spiral ganglion neurons in vitro. PLoS One. 2014; 9:e92157. DOI:10.1371/journal.pone.0092157
29. Kuffler DP, Reyes O, Sosa IJ, Santiago-Figueroa J. Neurological recovery across a 12-cm-long ulnar nerve gap repaired 3.25 years post trauma: case report. Neurosurgery. 2011; 69:E1321-E1326. DOI:10.1227/NEU.0b013e31822a9fd2
30. Lee SK, Lim YM, Lew DH, Song SY. Salvage of Unilateral Complete Ear Amputation with Continuous Local Hyperbaric Oxygen, Platelet-Rich Plasma and Polydeoxyribonucleotide without Micro-Revascularization. Arch Plast Surg. 2017; 44:554-558. DOI:10.5999/aps.2017.00451
31. Li L, Cai J, Yuan Y, et al. Platelet-rich plasma can release nutrient factors to promote facial nerve crush injury recovery in rats. Saudi Med J. 2019; 40:1209-1217. DOI:10.15537/smj.2019.12.24747
32. Mandour MF, Elsheikh MN, Khalil MF. Platelet-Rich Plasma Fat Graft versus Cartilage Perichondrium for Repair of Medium-Size Tympanic Membrane Perforations. Otolaryngol Head Neck Surg. 2019; 160:116-121. DOI:10.1177/0194599818789146
33. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998; 85:638-646. DOI:10.1016/s1079-2104(98)90029-4
34. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP?. Implant Dent. 2001; 10:225-228. DOI:10.1097/00008505-200110000-00002
35. Mohamad SH, Khan I, Hussain SS. Is cartilage tympanoplasty more effective than fascia tympanoplasty? A systematic review. Otol Neurotol. 2012; 33:699-705. DOI:10.1097/MAO.0b013e318254fbc2
36. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. Emerging roles for platelets as immune and inflammatory cells. Blood. 2014; 123:2759-2767. doi:10.1182/blood-2013-11-462432
37. Omar NN, El-Tawdi AH, Tash RF, Shoukry Y, Mahmoud NA, El Bakly W. Tumor potential in rat wounds after short- and long-term administration of platelet-rich plasma. J Biol Regul Homeost Agents. 2017; 31:889-899.
38. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013; 200:373-383. DOI:10.1083/jcb.201211138
39. Ricci E, Riva G, Dagna F, Cavalot AL. The use of platelet-rich plasma gel in superficial parotidectomy. Acta Otorhinolaryngol Ital. 2019; 39:363-366. DOI:10.14639/0392-100X-2093
40. Sánchez M, Anitua E, Delgado D, et al. Platelet-rich plasma, a source of autologous growth factors and biomimetic scaffold for peripheral nerve regeneration. Expert Opin Biol Ther. 2017; 17:197-212. DOI:10.1080/14712598.2017.1259409
41. Sankaranarayanan G, Prithiviraj V, Kumar R V. A Study on Efficacy of Autologous Platelet Rich Plasma in Myringoplasty. Otolaryngology Online Journal 2013; 3:1–15.
42. Scala M, Mereu P, Spagnolo F, et al. The use of platelet-rich plasma gel in patients with mixed tumour undergoing superficial parotidectomy: a randomized study. In Vivo. 2014; 28:121-124.
43. Schwieger J, Warnecke A, Lenarz T, Esser KH, Scheper V. Neuronal Survival, Morphology and Outgrowth of Spiral Ganglion Neurons Using a Defined Growth Factor Combination. PLoS One. 2015; 10:e0133680. DOI:10.1371/journal.pone.0133680
44. Shawky M. Management of Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) Intratympanic Platelet-Rich Plasma (PRP) Versus Intratympanic Steroid Injections: A Cross-Sectional Study. Otolaryngol Pol. 2024; 78:1-6.
45. Sheehy JL, Anderson RG. Myringoplasty. A review of 472 cases. Ann Otol Rhinol Laryngol. 1980; 89:331-334. DOI:10.1177/000348948008900407
46. Shen YP, Li TY, Chou YC, et al. Comparison of perineural platelet-rich plasma and dextrose injections for moderate carpal tunnel syndrome: A prospective randomized, single-blind, head-to-head comparative trial. J Tissue Eng Regen Med. 2019;13:2009-2017. DOI:10.1002/term.2950
47. Sherif AMH, Alawady MK, Mahfouz RM, Abbas AI, Ali HF. Comparative Study between Intratympanic Steroid Injection and Intratympanic Platelet Rich Plasma (PRP) Injection in Sudden Sensorineural Hearing Loss (SSNHL). Al-Azhar International Medical Journal. 2024; 5. DOI:10.58675/2682-339X.2385.
48. Shiomi Y, Shiomi Y. Surgical outcomes of myringoplasty using platelet-rich plasma and evaluation of the outcome-associated factors. Auris Nasus Larynx. 2020; 47:191-197. DOI:10.1016/j.anl.2019.06.005
49. Singh CV, Jain S. The Role of Platelet-Rich Plasma in the Management of Sensorineural Hearing Loss: Current Evidence and Emerging Trends. Cureus. 2024; 16:e68646. DOI:10.7759/cureus.68646
50. Sluga M, Battelino S, Vozel D. Prospects of Extracellular Vesicles in Otorhinolaryngology, Head and Neck Surgery. Journal of Nanotheranostics. 2021; 2:208-223. https://doi.org/10.3390/jnt2040013

51. Soares VY, Atai NA, Fujita T, et al. Extracellular vesicles derived from human vestibular schwannomas associated with poor hearing damage cochlear cells. Neuro Oncol. 2016; 18:1498-1507. DOI:10.1093/neuonc/now099
52. Steiner N, Battelino S. Extracellular vesicles and their use in inner ear. In: Kralj-Iglič, V. (Ed). Socratic lectures : 4th international minisymposium, Ljubljana, 11.-12. December 2020 : peer reviewed proceedings. Ljubljana: Zdravstvena fakulteta, 2021; pp: 167-172. Available on: https://www.zf.unilj.si/images/stories/datoteke/Zalozba/Sokratska_2021.pdf.
53. Steiner N, Vozel D, Urbančič J, Božič D, Kralj-Iglič V, Battelino S. Clinical Implementation of Platelet- and Extracellular Vesicle-Rich Product Preparation Protocols. Tissue Eng Part A. 2022; 28:770-780. DOI:10.1089/ten.TEA.2022.0024
54. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am J Sports Med. 2011; 39:2135-2140. DOI:10.1177/0363546511417792
55. Tao SC, Guo SC, Zhang CQ. Platelet-derived Extracellular Vesicles: An Emerging Therapeutic Approach. Int J Biol Sci. 2017; 13:828-834. DOI:10.7150/ijbs.19776
56. Tom SM, Sachdeva K, Kabade MV, Shukla A, Raj LV. Clinicoaudiological evaluation of hearing improvement in patients with sensorineural hearing loss using intratympanic platelet rich plasma versus steroid injection. Int J Otorhinolaryngol Head Neck Surg. 2022; 8:327-32. DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20220799
57. Troha K, Vozel D, Arko M, Bedina Zavec A, et al. Autologous Platelet and Extracellular Vesicle-Rich Plasma as Therapeutic Fluid: A Review. Int J Mol Sci. 2023; 24:3420. DOI:10.3390/ijms24043420
58. Tsai SC, Yang KD, Chang KH, et al. Umbilical Cord Mesenchymal Stromal Cell-Derived Exosomes Rescue the Loss of Outer Hair Cells and Repair Cochlear Damage in Cisplatin-Injected Mice. Int J Mol Sci. 2021; 22:6664. DOI:10.3390/ijms22136664
59. Tyagi BPS, Rout M, Head Platelet Rich Plasma (PRP): A Revolutionary Treatment of Sensorineural Hearing Loss. Acta Oto-Laryngologica 2019; 1:1.
60. Vozel D, Božič D, Jeran M, et al. Autologous Platelet- and Extracellular Vesicle-Rich Plasma Is an Effective Treatment Modality for Chronic Postoperative Temporal Bone Cavity Inflammation: Randomized Controlled Clinical Trial. Front Bioeng Biotechnol. 2021; 9:677541. DOI:10.3389/fbioe.2021.677541
61. Zhuang P, Phung S, Warnecke A, et al. Isolation of sensory hair cell specific exosomes in human perilymph. Neurosci Lett. 2021; 764:136282. DOI:10.1016/j.neulet.2021.136282
62. Zwierz A, Masna K, Burduk P, Hackenberg S, Scheich M. Renewed Concept of Mastoid Cavity Obliteration with the Use of Temporoparietal Fascial Flap Injected by Injectable Platelet-Rich Fibrin after Subtotal Petrosectomy for Cochlear Implant Patients. Audiol Res. 2024; 14:280-292. DOI:10.3390/audiolres14020025
63. Warnecke A, Harre J, Staecker H, et al. Extracellular vesicles from human multipotent stromal cells protect against hearing loss after noise trauma in vivo. Clin Transl Med. 2020; 10:e262. DOI:10.1002/ctm2.262
64. Wong EHC, Dong YY, Coray M, Cortada M, Levano S, Schmidt A, et al. Inner ear exosomes and their potential use as biomarkers. PLoS ONE.2018; 13:e0198029. https://doi.org/10.1371/journal.pone.0198029
65. Yadav SPS, Malik JS, Malik P, Sehgal PK, Gulia JS, Ranga RK. Studying the result of underlay myringoplasty using platelet-rich plasma. J Laryngol Otol. 2018; 132:990-994. DOI:10.1017/S0022215118001846
66. Yurtsever KN, Baklaci D, Guler I, et al. The Protective Effect of Platelet Rich Plasma Against Cisplatin-Induced Ototoxicity. J Craniofac Surg. 2020; 31:e506-e509. DOI:10.1097/SCS.0000000000006645