NARRATIVE REVIEW

Implication of stem cells and platelet rich plasma in otolaryngology, head and neck surgical procedures

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Abstract

Human body has a set of unspecialized cells called as stem cells that have the ability to generate cells of specialized function. Volume of fractionated plasma extracted from autologous blood is termed as Platelet-rich plasma (PRP) that is rich in several growth factors. Both have shown effective results in the field of regenerative medicine. Physiologically, platelets are the first cells to concentrate at the site of tissue damage, therefore application of PRP in diverse surgical procedures enhances bone and soft tissue healing; this same phenomenon is currently being used in otology, head and neck flap surgery and yielding miraculous outcomes. The perspective role of stem cells in regenerative medicine is wrapped in its loosely arranged DNA with working genes; a similar concept is being worked upon in different ENT procedures with groundbreaking results. But still, the data is scarce and there is a dire need for clinical trials, and large population-level studies to further formulate the guidelines on basis of proven evidence.

Keywords: Stem cell, platelet, plasma, otolaryngology, neoplasms

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Introduction

Since the start of the 21st century, the field of medicine has shifted its focus to better and effective healing that is in accordance with minimal complications, early healing, and cost-effectiveness. Stem cells and PRP have shown significant results in terms of regenerative medicine and effective healing in many sub-specialities of medicine and surgery but their role in otolaryngology and head neck cancer is relatively avant-garde; this narrative review is focussed on the use of stem cells and PRP in different subdomains of ENT, head and neck surgery.

Stem cell- Past, Present and Future implications

Pluripotent stem cells (PSC) form cells of embryonic germ layers only, therefore, synonymously termed as embryonic stem cell (ESC). Induced pluripotent stem cells (iPSC) are formed from the epiblast layer of the implanted embryo, and can also be artificially generated, for a promising future in regenerative medicine[1]. This pluripotency of stem cells makes them a potential therapy for use in regenerative medicine[2].

The potential role of stem cells in regenerative medicine is wrapped in its loosely arranged DNA with working genes. Normally, various signaling pathways, activate certain genes for the function of specialization while inactivating unimportant genes. Interaction in gene sequencing can reverse this process and give researchers a window for possible stem cell therapies, such as few tested in heart failure[3], retinal and macular degeneration[4], tendon ruptures, and diabetes type 1[5]. Haematopoietic stem cell (HSC) transplantation has been studied for more than 50 years. HSCs are extracted from the bone marrow, peripheral blood, or umbilical cord blood[6], and are useful in treating conditions such as leukaemia and anaemia.

As ideal as it may seem, stem cell therapy has several impediments. Out of all, human embryonic stem cells (hESC) remain an ethically debatable source of the cell. Secondly, uncontrolled proliferation of cells must be assessed before implanting stem cells in living patients[7] this tumorgenicity limit the use of iPSC, possibly due to the risk of oncogenes expression when reprogrammed.

Platelet-rich plasma therapy - future or trend

PRP was initially developed in the 1970s and first used in Italy in 1987 in an open-heart surgery procedure. Physiologically, platelets are the first cells to concentrate at the site of tissue damage, therefore application of PRP in diverse surgical procedures enhances bone and soft tissue healing. The platelets comprise of alpha granules that has growth factors, such as platelet-derived growth

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Table : Main functions of the growth factors present in platelet rich plasma.

Growth factors	Main Function
PDGF	– Increases hair growth – Vascularization – Angiogenesis stimulator
TGF-β	– Inhibits hair growth in vitro – Hair-cell proliferation and regeneration
VEGF	– Expressed in DP cells in the anagen phase – Probably regulates perifollicular angiogenesis – Increases perifollicular vessel size during the anagen growth phase
EGF	– Angiogenesis stimulator – Hair-cell proliferation and regeneration
HGF	– Angiogenesis stimulator
FGF	– Increases hair growth by inducing the anagen phase of HF – Promotes DP cell proliferation – Increases the HF size in mice – Angiogenesis stimulators
IGF-1	– Increases hair growth – Maintains HF growth in vitro – Angiogenesis stimulator

PDGF: Platelet-derived growth factor, TGF-β: Transforming growth factor beta, VEGF: Vascular endothelial growth factor, EGF: Epidermal growth factor, HGF: hepatocyte growth factor, FGF: Fibroblast growth factor, IGF-1: insulin-like growth factor 1

factor, vascular endothelial growth factor, epidermal growth factor, transforming growth factor-β and insulin-like growth factor (Table). Because of the ability to perform different functions and rejuvenate human tissue all these growth factors are valuable tools in regenerative medicine[8].

In last ten years , an exponential growth in several clinical trials evaluating PRP therapeutic effects on wound healing and renewal of soft tissue defects has been largely reported[9]. Platelet-rich plasma therapy has been extensively promoted for the local treatment of ligament injuries, osteoarthritis, and muscle tears[10].

Role of stem cells and PRP in Otology

The debate about stem cell therapy, platelet rich plasma and cloning is getting hysterical in terms of finding long-term treatment for hearing, balance, olfaction, and voice disorders[11,12]. The literature review with reference to otology shows, spiral ganglion can be an ideal target for stem cell therapy because the bony wall separating Rosenthal's canal from the perilymphatic space of the Scala tympani, is delicate and highly vascularized in humans. This intricate anatomical construction provides access to directly inoculate stem cells into the space of Rosenthal's canal where the spiral ganglion is located[13]. Another ability of stem cells is to form replacement hair cells for either the auditory or the balance receptors within the inner ear. This idea arises from the research into mammals such as reptiles, fish and birds who could regenerate hair cells following an injury[14,15]. In a study conducted by Yoshida et al in 2007, stem cells have shown to prevent hearing loss by regenerating hair cells through transplanted hair cells after an ischaemic insult[16,17].

The success rate of stem cell therapy is higher in uncomplicated systems where there are no compound linkages present between multiple different cell types. An obstacle in otology is the complex anatomy of the ear, which increased risk of causing trauma to adjacent structures and lead to more risk than benefit as a method of treatment[11]. Currently, one of the most successful research is being done on the capability of a patient's own cell to differentiate into new ganglia along with exerting a paracrine effect on the remaining spiral ganglion cells to produce replacement neurons from resident endogenous stem cells and/or to stimulate the repair and rehabilitation of damaged neurons and other cells types present within the damaged spiral ganglion[18,19]. Application of stem cell therapy in deficiencies of fibrocytes of the inner ear is also debatable. Transplanted mesenchymal stem cells are most likely to have both direct involvements by replacing into fibrocytes and by exerting a paracrine influence stimulating differentiation of nascent endogenous stem cells into replacement fibrocytes for recovery of damaged fibrocytes[20].

Sensorineural hearing loss is a disease of the ear caused by injury to the pathway for sound impulses from the hair cells of the inner ear to the auditory nerve[21,22]. Over the period of the last 5 years, multiple published studies have verified PRP to be a safe method to treat sensorineural hearing loss previously not resolved by medical management by promoting growth factors that lead to hair cell formation. This opens up many avenues for future research[23-25]. Another area where PRP is acting as a magic glue is the treatment of ear drum perforations, it has been observed that during the process of grafting if PRP is applied towards its edges it not only heals the damage better but also reduces the healing time and complications[26-28].

Role of stem cells and platelet rich plasma in Rhinology

Platelet-rich plasma (PRP) and platelet rich fibrin (PRF) are the two frequently studied autologous materials in rhinological procedures, while the potential role of Leukocyte- and Platelet rich fibrin (L-PRF), a second-generation platelet concentrate, is studied only in endoscopic CSF leak repair.

Growth factors particularly platelet derived growth factors (PDGF) and transforming growth factor beta (TGF-β) contribute to rapid wound healing and decrease scarring and haemostasis.[29] Platelet-rich fibrin (PRF) which is prepared by centrifuging the patient's blood at a lower speed forms a smooth gel that stays in place, while PRP remains liquid. Furthermore, centrifuging PRF at 3000rpm for 10min, Leukocyte and platelet rich fibrin (L-PRF) forms, that can abruptly aid in rapid mucosalization. A survey postulated that administration of PRP-soaked nasal packs not only accelerates healing but also reduces bleeding, and is proven to be effective in surveillance of inserted diced cartilage after rhinoplasty[30].

Bruising, nasal and pre-orbital oedema are some common postoperative complications following rhinoplasty. A prospective study concluded that 26.3% of the PRP group had nasal oedema as compared to 52.6% in the non-PRP group[31]. Skin necrosis, one of the rare complications following rhinoplasty, was also successfully managed with purified PRP mixed with autogenous fat graft[32]. In long-term follow-up, PRF has reliable aesthetic result. Studies done on septorhinoplasty patients; implanted split cartilage grafts were wrapped in PRF matrix, had reduction in ecchymosis, oedema and successful results in dorsal grafting and tip area after 4-22 weeks of follow-up period as compared to the first week after operation [33]. This not only clinched PRF matrix to be an easy-to-prepare and ready-to-use biocompatible material but also a potential alternative to reduce the need for a second surgical incision (in case of temporalis fascia), and risk of infection (in case of Surgicel)[34]. Moreover, the rate of epithelial regeneration and fibroblast proliferation was statistically significant ($p = 0.048; 0.021; 0.046$) in patients undergoing septoplasty when done in conjunction with PRP[35]. Application of PRF on nasal mucosa resulted in 89.2% of patients being norm osmic in the first postoperative week[36]. Injecting PRP in the olfactory cleft is however novel in recovery of smell. These effects on nasal mucosa demonstrated PRP as a ground-breaking biogenic stimulator which can be used as a less invasive approach to treat atrophic rhinitis, as the improvement in patients' nasal symptoms and mucociliary clearance are similar to the results obtained by routine invasive approaches i.e., adipocyte-derived stem cells dermo fat grafts[37].

In cerebrospinal fluid leak, either spontaneous or acquired, L-PRF can be used as an actual layer for repair through an endoscopic approach. This helps to use a smaller number of grafts in the traditional multi-layer repair process. Besides being a cost-effective autograft, L-PRF completes mucosalisation at the surgical site in 3-4 weeks with less chance of recurrence, and no donor site jeopardisation[38]. There is also a reduction in the rate of local or systemic postoperative infection as L-PRF has bactericidal properties[39]. When applied locally, PRP has also shown improvement in symptoms among patients with recurrent sinusitis/polyposis[8]. Staph Aureus is detected in 50% of patients with chronic sinusitis, and as PRP has antibacterial effects, PRP can be used as sinus lavage in endoscopic sinus surgeries or synergistically with beta-lactam antibiotics[40]. These outcomes can theoretically be justified as PRP increases the number of platelets in the wound area, promoting the number of growth factors or in the case of PRF, increasing fibroblastic proliferation induce angiogenesis thereby collecting circulating stem cells in the blood, ultimately increase osteoblastic activity and stimulates bone regeneration in the peri-implant area. PRF has the characteristic of polymerising, it protects growth factors from proteolysis, implying their availability for a longer period eventually aiding in the handling of graft material[19] and improving quality of life in general[41].

Role of stem cells and PRP in Laryngology

Comparatively literature on the larynx is less and most of it is based on animal models. The common cause of acquired laryngotracheal stenosis is prolonged endotracheal intubation; 24% of cases involving children. The treatment so far is reconstruction with anterior or posterior costal cartilage grafting for the repair of moderate to severe laryngotracheal stenosis[42], and the success of this surgery lies in proper and effective wound healing that prevents restenosis. It has been observed that the direct application of growth factors can control the inflammatory response and enhance wound repair [43]. From previously published studies on animal models, it has been proven that local application of PRP enhances the growth factors and minimises the inflammatory reaction that leads to better and more effective wound healing[41].

Another pathology associated with the larynx is vocal cord scar or atrophy. This in turn results in dysphonia and altered pitch. A pioneer case report published by Bhatt NK et al. was based on the local application of PRP in the vocal cord which in turn led to significant improvement in the voice within 4 months[44]. Another animal-based study worked sample of 24 mice with vocal cord injury, determined that it leads to accelerated epithelisation of injured rat vocal folds by inducing EGFR secretion[45]. Ujvary LP et al and Woo et al further studied the effects of PRP in a series of cases and including the patients having temporary vocal cord palsy and yielded promising results[42]. Tsou YA et al worked on one of the most

common causes of glottic insufficiency: Sulcus vocalis which results in incomplete vocal fold closure during phonation. PRP proved to enhance the survival of autologous fat, which is the main choice of treatment in sulcus vocalis[46]. In regard to stem cells, no published literature is available.

Use of stem cells and PRP in head and neck surgeries

Platelet rich plasma are a rich source of various platelet-derived growth factors (PDGF), that cause neo angiogenesis and help in wound healing[47]. Platelet rich plasma (PRP) has proven to be a convenient and low-cost method to prevent the incidence of post-surgical complications[48]. The role of PRP has been well established among other specialties like maxillofacial surgery and plastic surgery[49]. But its use in head and neck surgery is still in evolving phase.

Many patients who undergo head and neck surgeries have a history of radiotherapy, which can cause complications like wound dehiscence, oro-cutaneous and oro-cervical fistulas. Along with radiotherapy, comorbidities like ischaemic heart disease and diabetes mellitus, or risk factors like tobacco chewing and smoking render the tissue hypoxic and hypo-vascular that later leads to multiple surgical-related complications[50]. Bramati et al. have published a case series where platelet rich plasma was injected to treat post-operative fistula formation. These patients also received postoperative radiotherapy as part of the treatment[48].

Another important aspect of head and neck surgery are flaps; for example, pectoralis major or free fibular flaps to reconstruct soft tissue or bone defects. Once flap is harvested, the donor site is covered with a split-thickness or full-thickness skin graft[51]. Multiple applications of PRP can also be used to escalate the healing process of the donor site[52-53]. Lindeboom et al inducted 10 patients who underwent bilateral autologous iliac crest bone as an on-lay graft for maxillary reconstruction. He injected PRP on one side of the mouth and left the other to heal without PRP. The study concluded that PRP had a strong stimulant effect in neovascularization that escalated the healing process[54]. Marx et al inducted 88 patients with mandibular tumours, both benign and malignant, and concluded that the grafts with PRP showed greater trabecular bone density than non-PRP grafts at 6 months. Also, grafts with PRP performed well on graft maturity index at 2, 4 and 6 months[9].

Although PRP in head and neck surgeries has proved its importance in rapid wound healing and preventing several wound complications, the method to use PRP is not standardized. It varies from being injected into the wound or applied topically in the form of gel, or even injected after mixing with the fat[55].

Conclusion

As has been discussed, PRP and stem cells have a very beneficial role in ENT surgeries but the data available lacks proven evidence. Therefore, clinical trials, and large population-level studies are needed to further formulate the guidelines on its use. This will help bridge the gap between surgical application and academic basis of PRP and stem cells.

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