REVIEW ARTICLE

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Research progress of platelet-rich fibrin in alveolar ridge preservation

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INTRODUCTION

The alteration of the hard- and soft-tissue contour after tooth extraction has been studied extensively. Research has found that significant changes in the alveolar bone and surrounding tissues occur after the extraction of natural teeth[1]. Particularly in the upper jaw, a large amount of bone loss occurs during the natural healing process after tooth extraction, resulting in changes in the three-dimensional shape of the alveolar bone[2]. These changes bring difficulties to later implant restoration, and complex soft- and hard-tissue incremental surgery is often required to compensate for tissue defects[3]. Even though different treatments have been attempted to reduce or avoid surrounding tissue defects caused by tooth loss, studies have failed to identify a technique that compensates for that issue[4]. Therefore, finding a safe and inexpensive biological material for alveolar ridge preservation is a common goal in current research.

Biological additives, such as platelet concentrates, have also been proposed as adjunctive therapies for bone regeneration. As a second-generation blood concentrate, platelet-rich fibrin (PRF) is rich in platelets and various cytokines (which can effectively promote the regeneration of soft and hard tissues) and has the advantages of low cost and easy preparation[5]. In addition, the preparation of PRF does not require the addition of anticoagulants, and all components originate from the body, which eliminates ethical controversy. At the same time, its three-dimensional structural features increase its stability, making it suitable for long-term use[6]. Randomized controlled studies have shown that the use of L-PRF as a socket filling material to achieve the preservation of horizontal and vertical ridge dimensions 3 months after a tooth extraction is beneficial[7].

This article aimed to review the development history, application prospects, and research results of soft tissue and alveolar bone PRF in order to provide theoretical support for the clinical application of PRF.

METHODS

We searched the PubMed database for English-language articles in peer-reviewed journals that were published between April 1995 and December 2020 using the terms "platelet concentrates," "platelet-rich plasma," and "platelet-rich fibrin." We checked the relevance of the titles and abstracts of the 4,025 articles searched. We reviewed and presented the development of platelet concentrates. Then, the PubMed database was searched using the terms "platelet-rich fibrin," "alveolar bone," and "application." Randomized, double-blind, placebo-controlled trials (RCTs) with results reported as intention-to-treat analyses were considered the highest quality data. Large prospective cohort studies, meta-analyses, and systematic literature reviews were also included as appropriate for supplementing the RCT results. There were no specific inclusion or exclusion criteria. The reference lists of retrieved reviews were searched for additional articles, and the relevant references from retrieved articles were also evaluated. The effects of PRF on alveolar ridge preservation and soft-tissue protection are discussed below with reference to these documents (Figure 1).

DEVELOPMENT HISTORY OF PLATELET CONCENTRATES

The development history of platelet concentrates can be traced back to the 1980s and 1990s. They first appeared in the form of platelet-rich plasma (PRP). However, the preparation process is complicated, and it requires the addition of heterologous thrombin and anticoagulant; this increases the risk of immune rejection and cross infection and hinders the formation of blood coagulation and fibrin clots, thus limiting its application in the treatment of tooth extraction sockets[8].

In 2000, Dr. Choukroun[9] developed a new preparation technology using a 100% natural method (without anticoagulants or thrombin) to formulate a new generation of platelet-concentrate PRF. A comparison of the most important characteristics of PRP and PRF is presented in Table 1.

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Comparing the performances of PRP and PRF, we can see that PRF is more efficient with better characteristics than PRP. PRF has broad application prospects for the treatment of tooth extraction sockets.

PRESERVATION EFFECT OF PLATELET-RICH FIBRIN ON THE ALVEOLAR BONE IN SITE PRESERVATION

After a natural tooth is extracted, due to the loss of blood supply to the periodontal ligament, the alveolar bone will undergo rapid absorption and reconstruction[10,11]. In 2013, Professor Hauser and his team reported that PRF could induce the formation of new bone in the extraction socket. A micro-computed tomography (CT) analysis showed that in the PRF group, the alveolar socket had higher bone density and more bone trabeculae with better trabecular spacing; the healed bone formed a better microstructure with a more ideal bone quality, and the width of the alveolar ridge was well preserved[12].

Yüce and Kömerik selected 40 patients with alveolar osteitis following third molar extractions to observe the soft-tissue healing rate using the modified index of Landry, Turnbull,

Table 1. Overview of important characteristics of two blood products (platelet-rich fibrin and platelet-rich plasma).

Blood products	PRF (2000)	PRP (1998)
Protocol	Easy	complex
Speed rate	Fast	Slow
Reproducibility	No bias	Possible bias
Use of anticoagulants	No	Yes
Amount obtainable	Good	Enough
Costs of the protocol	Low	High
Amount of fibrin obtainable	High	Low
Speed of fibrin formation	Physiological	High
Fibrin morphology	Trimolecular	Tetramolecular
Leukocytes amount (%)	65	0–50
Immunomodulatory properties	Yes	Poor
Neo-angiogenic potential	+++++	+
Osteoconductive potential (scaffolding)	High	Poor
Mechanical properties (sol-gel-membrane)	Good	Enough
Presence of MSCs	Yes	Yes

PRF: platelet-rich fibrin; PRP: platelet-rich plasma; MSCs: mesenchymal stem cells.

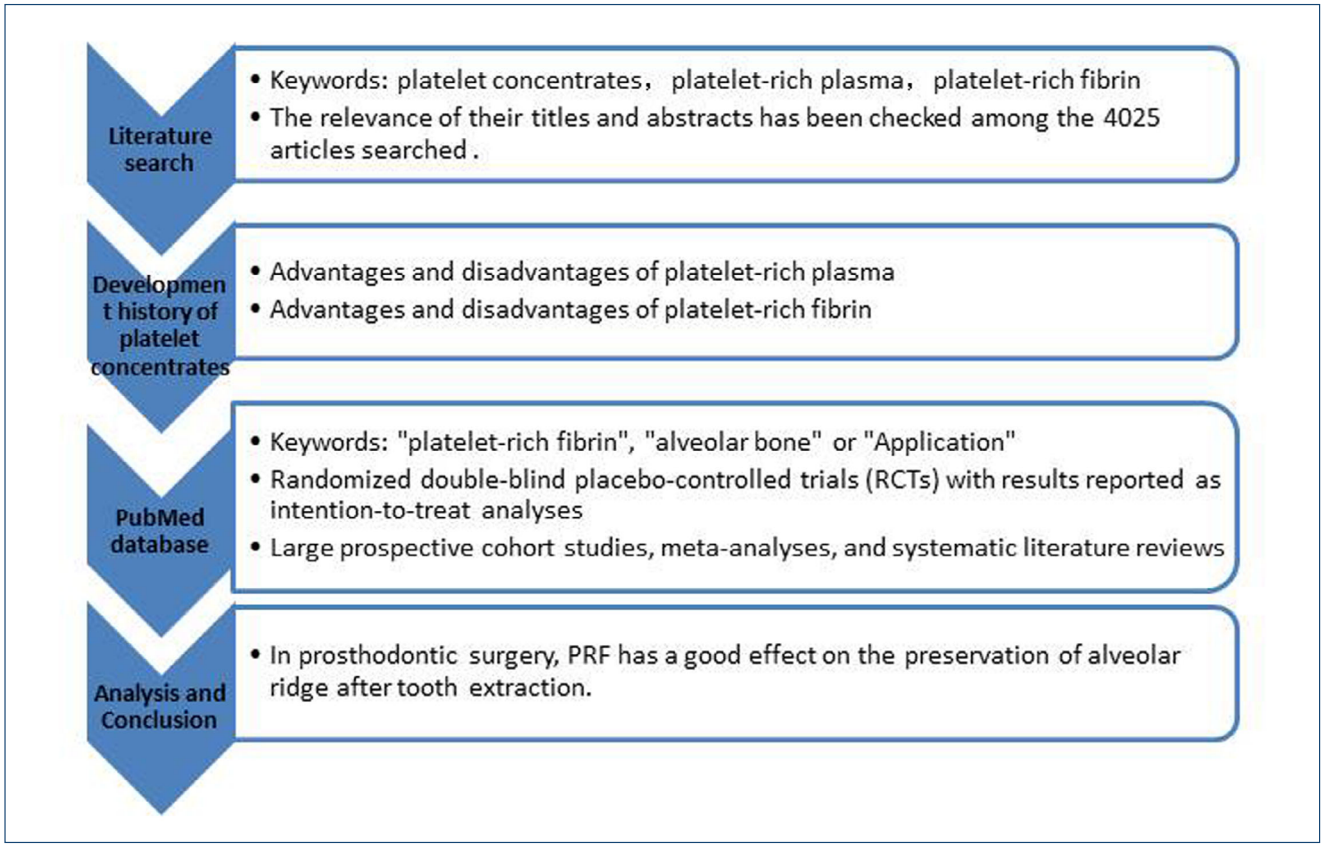

Figure 1. Platelet-rich fibrin related information.

and Howley. The results revealed that, after PRF treatment, the healing rate of epithelial tissue was significantly faster than in patients who had not received PRF treatment[13].

A clinical trial conducted by Professor Das compared PRF and β-tricalcium phosphate collagen (β-TCP-Cl) as a single-root alveolar socket transplantation material for the treatment of extraction sockets. Both materials had a fast replacement rate, but histologically, β-TCP-Cl showed higher bone density and tissue maturity; at the same time, it had less medullary space. The study showed that PRF offers comparable alveolar ridge preservation and reduction of alveolar bone resorption, especially for buccal bone plates (PRF: 1.5-mm bone loss; β-TCP-Cl: 0.99-mm bone loss)[14].

In 2016, Andwandter reported the healing of the extraction socket after filling with PRF. Immediately after tooth extraction and again after 4 months, personalized acrylic scaffolds were used for bone detection, and cone-beam CT (CBCT) was used to obtain imaging measurements. It was clinically observed that the alveolar ridge top absorbed (1.18±2.4 mm) horizontally, and there was a bone loss of 1.25±2.0 and 0.83±2.0) mm at 2 and 4 mm of the root of the ridge, respectively. The vertical bone resorption of the buccal bone plate was 0.44±3.5 mm. The imaging analysis showed that the buccal bone plate lost 0.27±2.5 mm perpendicular to the bone and 0.03±1.6 mm to the tongue. The width of the alveolar ridge was reduced by 1.33±1.43 mm. These results were similar to those of a systematic review in which buccal bone plate resorption was 0.5–1 mm after the application of bone-graft materials[15].

Temmerman et al. studied the effect of PRF as a filling material for alveolar ridge preservation. This study included patients with single-jaw bilateral symmetrical tooth extraction, and CBCT examinations were performed on day zero and again after 3 months. At the time node, the average alveolar ridge width difference was measured at three levels below the top of the buccal lingual alveolar ridge (1 mm below the top of the ridge [main observation variable] and 3 and 5 mm below the top of the ridge). At 1 mm below the ridge, the reduction in the alveolar bone width between experimental group (-22.84%) and control group (-51.92%) was statistically different ($p<0.005$). There was a statistically significant difference in the amount of filling in the extraction socket (visible mineralized bone) between experimental group (94.7%) and control group (63.3%)[7].

Wang Binping et al. took 30 patients with extracted posterior teeth as research sample. Immediately after extraction, the alveolar socket was filled with PRF for site preservation. CBCT was performed for 4–6 months to observe the changes in the height and width of the alveolar bone. The conclusion was that PRF site preservation technology could well preserve the height and width of the alveolar bone in the posterior tooth area, which was conducive to later implant restoration[16]. At the same time, the application of PRF in the preservation of tooth extraction sites could accelerate wound healing, inhibit the absorption of the patient's alveolar ridge, and lay the foundation for the implementation of subsequent dental implants[17].

The fibrin network of PRF can maintain red blood cells to slowly release growth factors, including transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor, and insulin-like growth factor-I (IGF-I)[18]. Among these, TGF-β1 can promote the rapid proliferation of oral cells, and PDGF can regulate the migration, proliferation, and survival of mesenchymal cells. VEGF plays an important role in angiogenesis and the reconstruction of damaged tissue. Finally, IGF-I is a regulatory factor for a variety of cell proliferation and differentiation processes (Table 2).

Thus, after a natural tooth is extracted, the application of PRF can maintain the slow release of growth factors from red blood cells through the formed fibrin network, inhibit the resorption of the patient's alveolar ridge, and induce the

Table 2. Platelet therapy growth factor functions.

Platelet-derived growth factor (PDGFaa, PDGFbb, PDGFab)	Triggers the activities of neutrophils, fibroblasts, and macrophages Chemoattractant/cell proliferator Stimulates mesenchymal cell lineages
Transforming growth factor (TGF-β1, TGF-β2, TGF-β3)	Promotes cellular differentiation and replication Stimulates matrix and collagen synthesis Stimulates fibroblast activity and collagen production
Vascular endothelial growth factor (VEGF)	… Angiogenesis … Stimulates synthesis of basal lamina
Fibroblastic growth factor (FGF)	Angiogenesis Fibroblast production
Epithelial cell growth factor (ECGF)	Stimulates epithelial cell replication
Insulin-like growth factor (IGF-1)	Promotes cellular growth and proliferation

formation of new bone in the extraction socket. At the same time, PRF can accelerate the healing of epithelial tissue. This lays the foundation for the implementation of subsequent dental implants.

PRESERVATION EFFECT OF PLATELET-RICH FIBRIN ON SOFT TISSUE IN SITE PRESERVATION

PRF has been proven to continuously stimulate the proliferation of gingival fibroblasts, osteoblasts, and periodontal ligament cells[19]. At the same time, PRF can promote soft-tissue regeneration by releasing PDGF and TGF-β[20]. Therefore, PRF has great potential for promoting the healing of soft tissues around extraction sockets and enhancing aesthetic repair.

Sybil et al. recruited 25 patients with bilateral surgical disimpaction of the mandibular third molar and placed them in PRF and no-PRF groups on the left and right sides of extraction wounds. The results showed that PRF has a significant effect on soft-tissue healing[21]. In recent years, Lv Min and other researchers in China have also confirmed the ability of PRF to promote soft-tissue healing. By placing PRF in the extraction wounds of 140 affected mandibular third molars and comparing the results with conventional blood-filled clots, it was found that 3 months after the operation, there were only three cases of adjacent tooth periodontal attachment loss in the PRF group, while there were 25 cases in the blood clot group, of which 3 cases were larger than 2 mm with infection. Experiments have proven that PRF can promote the restoration of adjacent teeth periodontal tissue[22].

In vivo research on the anterior soft-tissue defect model of a rabbit hard palate showed that PRF could accelerate soft-tissue wound healing and reduce scar formation[23]. PRF has a significant promoting effect on the proliferation of dermal fibroblasts via the mitosis and migration of dermal fibroblasts and soft-tissue reconstruction. At the same time, studies have found that PRF can promote the proliferation of fibroblasts and keratinocytes in the gums[24]. In addition, He et al.[25] used mass tissue culture to isolate and culture human gingival fibroblasts (HGFs). Using flow cytometry, the results showed that after the PRF treatment of HGFs, the proportion of HGFs in the S phase was significantly prolonged.

Liu et al. placed double PRF membranes in 46 and 47 implant surgery cases. A 5-month follow-up revealed that the width of the keratinized gingiva was significantly increased, and the colour and shape of the mucosa were clearly abnormal[26]. At present, PRF has also played an important role in clinical treatments in other medical fields. For example, when chronic venous ulcers of the lower extremities were covered with porous PRF film, in the subsequent 16 weeks of wound closure speed testing, the ulcers on 66.7% of patients had essentially healed[27].

In summary, the mechanism of PRF on soft-tissue repair may have the following causes. First, a large number of PDGF receptors can be found in periodontal tissue. PDGF can act as a chemokine for fibroblasts in the gingival periodontal ligament to promote soft-tissue regeneration. Second, TGF-β1 (produced by macrophages, fibroblasts, keratinocytes, and platelets) can promote the healing of skin wounds. In addition, PRF contains a large amount of VEGF, which promotes vascularization to support the regeneration of soft tissues, activate mitosis, and the migration of vascular endothelial cells, thereby activating the early vascularization of tissue repair and promoting the formation of soft tissues[28].

SUMMARY AND PROSPECTS

At present, denture implants are widely used in oral restorations, so it is very important to maintain a good three-dimensional shape of the alveolar socket after tooth extraction[29,30]. From a clinical application perspective, PRF has a significant alveolar ridge preservation effect and a good protective effect on the surrounding soft tissue. At the same time, since the material is derived from the recipient itself, it has good biocompatibility and no problems with immune rejection, and it can be considered a safer autologous biological material.

Despite the lack of strong evidence in the reviewed articles, the favourable effect of PRF on alveolar ridge preservation during natural tooth extraction and implantation procedures is evident. Given its ease of preparation, low cost, and biological properties, PRF can be considered a reliable treatment option. However, standardization of the protocol is required to obtain reproducible results. The use of enough PRF clots or membranes seems to be crucial to obtaining an optimal effect. Due to the lack of standardization in the study's design and variables analysed, further RCTs with long-term follow-up are needed to assess the beneficial effect of PRF on alveolar ridge preservation.

AUTHORS' CONTRIBUTION

SLH: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **HGZ:** Conceptualization, Data curation. **NL:** Formal Analysis, Writing – original draft. **XHZ:** Formal Analysis, Writing – review & editing. **HHC:** Formal Analysis, Writing – review & editing.

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