



Autologous blood derived cell therapy in maxillofacial bone graft surgery

Joo-Young Park

Department of Oral and Maxillofacial Surgery, Seoul National University Dental Hospital,
School of Dentistry, Seoul National University, Seoul, Korea

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Tissue regeneration is one of the ultimate goals of maxillofacial surgery and various types of tissue engineering technologies have been utilized in clinics. Healthy resources of host cells and growth factors are essential for the tissue engineering, therefore autologous blood-derived cell therapy was introduced. In this article, clinical applications of the autologous platelet concentrates and stem cell separation therapy will be summarized and evaluated for their efficacy and feasibility in the current maxillofacial clinics.

Key words: Tissue engineering, Regeneration, Maxilla, Mandible, Autografts

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I. Introduction

Bone graft in maxillofacial field is a procedure performed to increase the amount of alveolar or basal jaw bones where they have been lost by diseases, trauma, or surgeries. Because of the difficulties to regenerate the bony defects completely and rapidly, various types of tissue engineering technologies have been applied in maxillofacial clinics¹⁻⁴. For example, bone graft materials such as allogenic, xenogeneic, and synthetic bones were introduced and used as scaffolds, as well as barrier membranes and titanium mesh are available to facilitate proper three-dimensional (3D) shapes of bone formation. Importantly, one of the missing aspects in this endeavor is lack of healthy resources of host cells and growth factors, such as local mesenchymal stem cells or bone marrow progenitor cells with autologous growth factors. To overcome this limitation, autologous blood-derived cell therapy was introduced several decades ago consisting of platelet concen-

trates (PCs) such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). In addition to the PCs, closed system of stem cell separation from the patients' own bone marrow or blood was also developed and utilized in clinics. In this article, clinical applications of the autologous blood derived cell therapy will be summarized and evaluated for their efficacy and feasibility in maxillofacial surgery.

II. Types of Clinically Available Autologous Blood Derived Cell Therapy

1. Platelet-rich plasma

The concept of PCs was originated from the idea that platelets and autologous growth factors could be condensed in plasma and utilized to promote local wound healing⁵. The first generation of PCs was given the popular name PRP and is composed of over 95% platelets, a cell type that actively secretes growth factors for initiating wound healing and secreting factors responsible for enhancing cell adhesion, proliferation, and migration of various cell types⁶⁻⁸. However, PRP preparation requires addition of bovine thrombin or CaCl₂ which makes that PRP is not 100% autologous. Furthermore, the preparation must be centrifuged in two separate stages to increase purity of platelet concentration.(Fig. 1,

Joo-Young Park

Department of Oral and Maxillofacial Surgery, Seoul National University
Dental Hospital, School of Dentistry, Seoul National University, 101
Daehak-ro, Jongno-gu, Seoul 03080, Korea
TEL: +82-2-2072-4498

E-mail: bbyoung1@snu.ac.kr

ORCID: <https://orcid.org/0000-0002-0333-6349>

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left) It has further been reported that the liquid nature of PRP complicates its handling by clinicians. All these limitations have led to the emergence of a second-generation PCs.

2. Platelet-rich fibrin

PRF can be fabricated from 100% autologous sources without any bovine thrombin or CaCl_2 and can be fabricated by a one-step standardized method⁹⁻¹¹. Through centrifugation of peripheral blood, physiologic clot formation and fractioning are induced. The natural clot formation by centrifugation requires using specific tubes with a glass surface initiates the coagulation cascade and activates platelets during centrifugation. The resulting PRF consists of a fibrin scaffold that contains platelets, leukocytes, and plasma proteins. After centrifugation, the resulted 3D fibrin matrix of the PRF serves as a reservoir of growth factors and soft tissue barriers.(Fig. 1, middle)

3. Closed cell separation system for autologous bone marrow or whole blood

Efforts to separate blood cells, especially hematopoietic stem cells from patients' own blood have been made to utilize the stem cell fractions for tissue engineering. There are a multitude of ways to sort different types of cell components and one of the quicker ways to sort a sample based on physical

characteristics is density gradient centrifugation. However, the first trial to separate and transplant the autologous human bone marrow mononuclear cells was only conducted in 2001 for treatment of chronic heart disease and peripheral arterial disease using SEPAX system¹². Several companies developed commercially available closed centrifugation system to efficiently separate blood cell fractions aseptically to maintain the high standards required for cellular therapeutics¹³⁻¹⁵.(Fig. 1, right) Although transplantation of the stem cell fraction is efficient for tissue regeneration, statistics and official report from the Korean Ministry of Health and Welfare in 2018 showed that only 4 autologous or allogenic stem cell products have been approved and available in clinics among all 15 cell therapy products in South Korea. However, not a single cell therapy product is approved yet for dentistry and maxillofacial surgery field.

III. Controversies in Usage of Autologous Blood Derived Cell Therapy in Maxillofacial Surgery

1. Advantages

Numerous studies on PRP and PRF were published to show efficacy for their dental tissue regeneration, such as regeneration of periodontal bony defect, tooth furcation defect, gingival defect on tooth roots, extraction socket preservation and maxillary sinus membrane elevation^{8-11,16}. Autologous

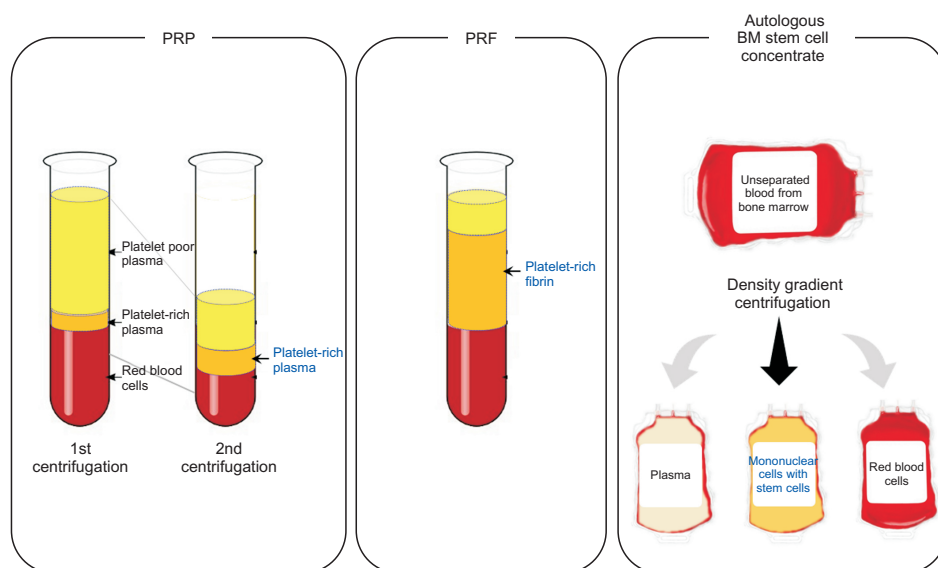


Fig. 1. The layers after centrifugation, the blood components and separated cells are shown among PRP (platelet-rich plasma; the most left), PRF (platelet-rich fibrin; middle) and autologous bone marrow (BM) stem cell concentrate (the most right). The final product from each preparation method is written in blue.

Joo-Young Park: Autologous blood derived cell therapy in maxillofacial bone graft surgery. *J Korean Assoc Oral Maxillofac Surg* 2021

stem cells separated from blood or bone marrow also have been showed superior soft tissue wound healing in dermatology, cardiology, and plastic surgery¹²⁻¹⁵. Furthermore, recent studies showed that platelets and mesenchymal stem cells promote tissue regeneration by modulating local immune reactions^{17,18}.

2. Disadvantages

Autologous blood-derived cell products require manipulation procedures *ex vivo*, so that there has been contamination, safety, and standardization issues for clinical application. Additionally, health technology assessment was first introduced in South Korea in 2006, and the Committee of New Health Technology Assessment (CNHTA) was formed and started to review safety and effectiveness of the new health technology. Since then, PCs in various medical applications tried to be approved as a new medical technology by CNHTA; however, no trial was succeeded until January 2019. Currently, autologous PRP application is approved for single usage in treatment of tennis elbow; Epicondylitis humeri radialis, and no other medical, dental, and maxillofacial usage is approved.

IV. Summary and Editor's Opinion

(1) Autologous blood-derived cell therapy can supply healthy resources of host cells and growth factors to promote tissue regeneration in maxillofacial surgery field.

(2) Although there have been controversies in efficacy and feasibility of PCs and stem cell transplantation, the autologous blood-derived cell therapy is one of the better options for regeneration of maxillofacial tissues.

(3) We need more *in vivo* and clinical trial data to find the proper therapeutic doses for autologous PCs and stem cells suitable for different clinical situations in maxillofacial surgery.

(4) Development of concrete and practical solutions including standardized clinical protocols, technologies and delivery systems of PCs and stem cell fractions will become essential in the future.

Author's Contributions

The manuscript was written by J.Y.P.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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