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Major randomized clinical studies of alopecia treatment with platelet-rich plasma: a systematic review

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Abstract

Introduction: Alopecia for men and women represents a significant problem worldwide, with around 600,000 hair restoration surgical procedures performed worldwide each year. Thus, the use of platelet-rich plasma (PRP) in regenerative medicine has been investigated for the treatment of alopecia. **Objective:** We performed a concise systematic review of the main clinical findings of the use of platelet-rich plasma for the treatment of alopecia. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from August to September 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 5 years were selected. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results:** PRP was effective in increasing the proliferative activity of hair follicle cells and in increasing capillary density. In androgenetic alopecia, the addition of PRP with microneedling increased effectiveness and shortened the time required for optimal results, as did the combined use of PRP and minoxidil. **Conclusion:** According to the results of the main randomized controlled trials, platelet-rich plasma showed efficacy in increasing the proliferative activity of hair follicle cells and increasing capillary density.

Keywords: Alopecia. Platelet-rich plasma. Hair follicle. Aesthetic. Randomized Clinical Studies.

Introduction

In the context of dermatological aesthetics, alopecia for men and women represents a significant problem worldwide. Estimates indicate that around 600,000 surgical hair restoration procedures are performed annually worldwide [1,2]. Traditional treatment strategies have been largely limited to pharmaceutical and surgical modalities [3,4]. In this sense, drugs such as finasteride and minoxidil require a high degree of compliance for long periods with varying degrees of effectiveness [1].

Still, there are side effects with the use of these drugs such as sexual dysfunction, mood disorders, increased risk of prostate and breast cancer, and birth defects [5,6]. Regarding surgical treatments, success and efficiency are affected by the surgeon's skill set, as follicular transection rates are limiting factors for both physician and patient [2,7]. In addition, the risk of scar formation, poor wound healing, and an unnatural hairline are often reported [8,9].

In this way, advances in molecular and cellular research allowed discoveries about the molecular pathways of the hair cycle, leading to cell-based therapies in hair restoration [10-13]. Thus, the use of platelet concentrates in regenerative medicine has been investigated for the treatment of alopecia [1]. In this aspect, platelet-rich plasma (PRP) is fundamental for wound repair and the inflammatory/remodeling pathway, as platelets contain several chemotactic and mitogenic agents, growth factors, proteins that are released upon activation, endocrine effects, and release of cytokines [2-4]. In addition, fact that PRP is autologous, the risk of hypersensitivity or immunogenic reactions is minimal.

Also in this context, once activated, platelets release alpha granules containing a myriad of growth factors, including transforming growth factor-β (TGF-β), epidermal growth factor (EGF), fibroblast growth factor, vascular endothelial growth factor (VEGF), plateletderived growth factor (PDGF), and insulin-like growth factor-1 (IGF1) [1].

Therefore, these factors have been considered important effects on the hair cell growth cycle, stimulating the proliferation, differentiation, and growth of the hair follicle. In this sense, the hair cycle consists of a resting telogen growth phase, active anagen, and apoptotic catagen phase [5,6]. The aberrations in the cycle of these phases allow an interruption in the growth of the hair follicle and consequent hair loss. In this aspect, the inducible stem cells found along the hair follicle axis are important to repopulate the hair follicle epithelium and are fundamental for the progression of the hair cycle [7]. These hair follicle stem cells present PRP growth factor receptors to stimulate hair growth and molecular pathway regulation [12,13].

In this scenario, important randomized controlled clinical studies have shown that the effects of PRP on hair restoration are promising. Therefore, the present study aimed to carry out a concise systematic review of the main clinical findings of the use of plateletrich plasma for the treatment of alopecia.

Methods

Study Design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis (www.prisma-statement.org/) were followed.

Data Sources And Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Alopecia. Platelet-rich plasma. Hair follicle. Aesthetic. Randomized Clinical Studies". The research was carried out from August to September 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Scientific articles from the last 5 years were selected. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality And Risk Of Bias

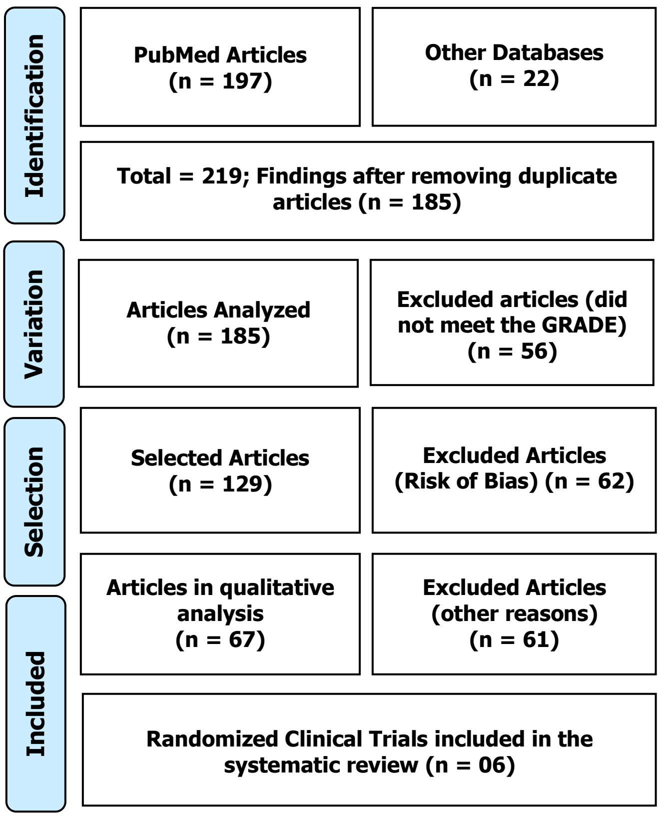
The quality of the studies was based on the GRADE instrument. The highest rankings were for randomized controlled trials, prospective or retrospective observational trials, meta-analysis studies, and statistically significant sample sizes (n>30 patients). The risk of bias was analyzed using the Cochrane instrument, based on the effect size of each study versus the sample size.

Results and Discussion

Summary Of Literary Findings

A total of 219 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 185 articles. A total of 67 articles were fully evaluated and 06 articles (randomized clinical trials) were included and developed in this systematic review study, as only randomized controlled trials were selected to compose the results section (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 62 studies at high risk of bias and 56 studies that did not meet the GRADE.

Figure 1. Flowchart showing the article selection process.



After reading and analyzing the main clinical studies selected in this study, an overall positive clinical response was observed to the use of PRP for hair restoration in patients with both androgenetic alopecia (AGA) and areata (AA). Furthermore, the use of PRP as an adjunct in hair transplantation, as well as the use with other adjunct technologies such as microparticles, CD34 cells, and microneedling can optimize the minimally invasive approach. Furthermore, when compared to traditional oral/topical treatments, identifiable complications are minimal and the desirability of treatment provides a positive outlook for future investigations. However, it is essential to promote the standardized implementation of protocols for the preparation and application of PRP for alopecia [1].

In this context, **Table 1** presents an overview of the role of growth factors in hair cell morphogenesis and hair cycle progression.

Table 1. Growth factors involved in the hair cycle.

TGF-β	✓ Development of placode and follicular architecture [14]; ✓ Induction of the anagen phase regulated by the Tsukushi signaling molecule [15]; ✓ Regulates endothelial chemotaxis and angiogenesis [16].
FGF	✓ Formation of the hair follicle precursor [17]; ✓ Induction and maintenance of anagen of the telogen phase via β-catenin [18].
VEGF	✓ Secreted by dermal papilla cells; ✓ Promotes angiogenesis and vessel permeability [16]; ✓ Essential during the anagen phase in follicle size [19,20].
PDGF	✓ Development of the dermal papilla from the epithelium [14]; ✓ Increases proliferation and is redundant throughout the cycle [21-23].
IGF-1	✓ Regulates cell proliferation and migration; ✓ Prevents the catagen phase [24,25].
EGF	✓ It promotes the proliferation of hair cells of the outer root sheath in the anagen phase [26].

Major randomized clinical studies

In this scenario, the present study described 06 important recent randomized controlled clinical studies that showed the effectiveness of the use of PRP in the treatment of alopecia. Thus, a randomized clinician performed a comparative assessment of the clinical efficacy of therapy with PRP, minoxidil, and their combination in the treatment of men with AGA and evaluated the effects of PRP on hair follicle (HF) cell proliferation in skin biopsy. The study involved 69 men divided into 3 groups who received therapy with PRP, minoxidil, and their combination. Treatment with PRP was more effective than treatment with minoxidil ($p=0.005$). Complex therapy was more effective than minoxidil monotherapy ($p < 0.0001$) and PRP monotherapy ($p = 0.007$). After the application of PRP, the absolute and relative values of the area of β-catenin and CD34 expression increased. An increase in the Ki67+ index was also significant [27].

Also, a randomized, double-blind, placebo-controlled trial compared safety, efficacy, and satisfaction after treatment with a lower or higher number of platelets over 6 months, involving 8 subjects with moderate AGA. Participants received intradermal injections of PRP (baseline and month 3). Both groups demonstrated absolute increases in total hair density, follicle diameter, and terminal hair density, as well as absolute and percentage changes in the frontal and crown target sites compared to the baseline [28].

In addition, another randomized placebo-controlled study investigated the effects of PRP on hair growth and thickness. Two 7.6 cm × 7.6 cm squares were tattooed on the scalps of 35 study participants with AGA. Areas were randomly assigned to intradermal injection with PRP or saline. Hair density in the PRP-treated area increased significantly compared to the baseline across all visits. At the final assessment, hair density in the PRPtreated areas increased from 151 ± 39.82 hairs/cm2 at baseline to 170.96 ± 37.14 hairs/cm2, an average increase of approximately 20 hairs/cm2 ($p<0.05$) [29].

Besides, a randomized controlled trial with 52 participants sought to clarify the molecular mechanisms underlying the action of PRP on hair growth. In addition to the human study, mouse and protein biochip models were used to explore the specific mechanisms of PRP that regulate hair growth. The results confirmed that PRP treatment boosted hair growth, and accelerated the hair cycle and the effect was sustained for more than one hair cycle in mice. Protein biochip evaluation confirmed remarkably upregulated β-Catenin, PDGF, and AKT signaling and repressed p53 signaling in the PRP injection group. Clinically, the mean hair count, density, diameter, and proportion of anagen hairs in the PRP group showed a significant improvement at 6 months compared to the control side [30].

Further, a randomized controlled trial evaluated the therapeutic effects of PRP on AGA. This study was done on 126 patients, 42 patients survived as a control group that received medical treatment, and only another 84 patients were subdivided into two groups, and received PRP sessions as adjunctive therapy by different administration methods. Patients treated with PRP had a statistically significant increase in hair density and diameter measurements than the control group. These results increased with the use of microneedling as a method of PRP administration [31].

Finally, a randomized, placebo-controlled study evaluated the effectiveness of PRP in promoting hair growth in patients with AGA. Five sessions were performed, measuring hair density and changes in hair caliber in 10 patients. At 16 weeks, 8 weeks after the last PRP injection, treated areas exhibited increased mean hair density (+12.76%) from baseline compared to placebo (+0.99%). The average hair caliber decreased in the treated and placebo regions (-16.22% and -19.46%, respectively). Overall, there was a positive correlation between glial cell line-derived neurotrophic factor (GDNF) concentration and hair density (p= 0.004). Although not statistically significant, they were also observed for FGF2 and VEGF [32].

Conclusion

According to the results of the main randomized controlled clinical studies, PRP was shown to be effective in increasing the proliferative activity of hair follicle cells and increasing capillary density. In androgenetic alopecia, the addition of PRP with microneedling increased effectiveness and shortened the time required for optimal results, as did the combined use of PRP and minoxidil.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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