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REVIEW ARTICLE

Meta-analysis of efficacy of platelet-rich plasma therapy for androgenetic alopecia

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ABSTRACT

Background: Platelet-rich plasma (PRP) therapy is used as an off-label treatment for androgenetic alopecia (AGA); however, published efficacy evidence is still preliminary.
Objective: Conduct a meta-analysis of current trial data to estimate efficacy.
Methods: Thirteen studies which investigated the use of PRP for treatment of AGA were identified from the literature. A meta-analysis was used to analyze results from four trials ($N = 60$) where sufficient quantifiable data extraction was possible. All 13 studies were analyzed qualitatively.
Results: When comparing PRP treatment to baseline, the overall standardized mean difference was 0.51 [95% confidence interval (CI): 0.14, 0.88; $I^2 = 0\%$] in favour of PRP treatment.
Conclusion: Preliminary results suggest that the investigation of PRP for the treatment of AGA is promising. Controlled trials with quantifiable measures of treatment success are now required to confirm these results.

Abbreviations: AGA: androgenetic alopecia; CI: confidence interval; DHT: Dihydrotestosterone; DP: dermal papilla; EGF: epidermal growth factor; FGF: fibroblast growth factor; IGF-1: insulin-like growth factor 1; PDGF: platelet-derived growth factor; PRP: platelet-rich plasma; TGF-β: transforming growth factor-β; VEGF: vascular endothelial growth factor

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platelet-rich plasma; androgenetic alopecia; hair restoration; growth factors; dermal papilla cells

Introduction

Platelet-rich plasma (PRP) is used as an innovative therapy in diverse fields including dentistry (1), surgery, orthopedics (2), dermatology and aesthetics (3). Currently, PRP preparation systems have FDA clearance for use in bone grafts and operative orthopedics (4) but off-label purposes such as for hair restoration have become increasingly common. PRP is a rich source of growth factors such as insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and fibroblast growth factor (FGF) which together can stimulate cell survival (5–8), proliferation (5), differentiation (5,9), vascularization and angiogenesis (10–12). Application of these growth factors to dermal papilla (DP) cells can lead to the initiation and prolongation of anagen phase in the hair follicle (5). Alpha granules within the platelets contain the growth factors and facilitate release at high concentrations, when the PRP preparation is activated (13).

Use of PRP in hair restoration has been investigated for multiple conditions including alopecia areata (14); however, the majority of research has been targeted towards androgenetic alopecia (AGA). AGA is the diffuse hair thinning which occurs in 40% of women or hair loss in the crown combined with an "M"-shaped hairline recession in 70% of men (15). Dihydrotestosterone (DHT) in sensitized areas of the scalp is believed to cause miniaturization of the hair follicle and lead to pattern hair loss (16). Outside of surgery, current approved therapy options include oral finasteride and topical minoxidil. Both are limited in that finasteride is not approved for use in women and is associated with undesirable side effects while use of minoxidil requires a long-lasting commitment to daily applications (17). Moreover, neither drug produces result in all patients (17), and efficacy is limited, especially in more severe, longer-term cases (18).

With more hair restoration clinics choosing to offer PRP therapy, data on treatment efficacy have begun to accumulate. The AGA application remains in the early stages as treatment protocols are still being refined. At this time, PRP has been used in combination with hair transplant surgery and as an injectable therapy alone. Furthermore, diverse methods are reported as activators can be used to stimulate growth factor release; additional components such as leukocytes and dalteparin and protamine microparticles may be included to boost results; and quantity and frequency of treatments have varied widely. Thus a meta-analysis of current data was performed to estimate the value of PRP therapy for treatment of AGA, while a literature review was used to identify essential protocol components.

Materials and methods

The PubMed and Google Scholar databases were searched using the terms "androgenetic alopecia" and "platelet-rich plasma" on 7 October 2015 and additionally on 22 March 2016. Fifteen unique studies which investigated the use of PRP as treatment for AGA were identified. The references of these studies as well as clinicaltrials.gov were also searched for relevant articles; however, additional data were not obtained.

There were two studies that examined PRP as a treatment for AGA outside of human subjects (e.g. *in vitro*, murine models), and thus will be described qualitatively. The remaining human studies will be described quantitatively in the form of a meta-analysis where possible. Of the 13 identified human studies, methods varied greatly. Therefore only studies using direct injections of PRP to

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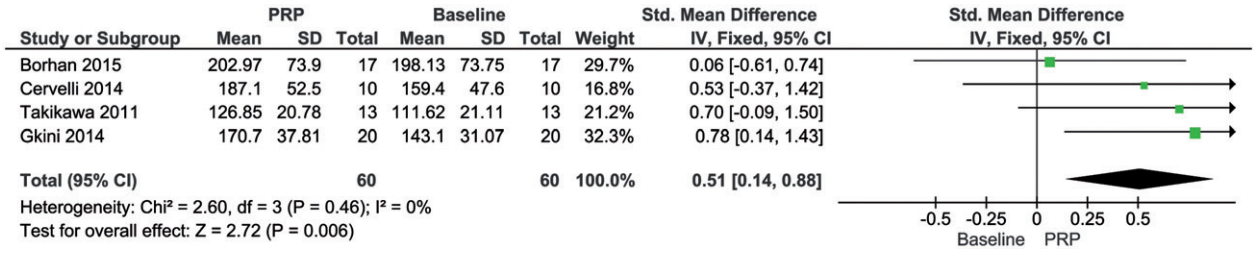

Figure 1. AGA treated with PRP. A forest plot is used to depict meta-analysis results of the efficacy of PRP therapy for AGA as compared with baseline. Four studies (pooled $N = 60$ participants) which used PRP injected directly into the scalp to stimulate hair growth in patients with AGA were compared using meta-analysis. Hair density was used as the measure of treatment success.

the scalp were considered for inclusion in the meta-analysis. Additionally, measures of treatment success were diverse, many of which used subjective evaluations. Further studies were excluded due to an absence of quantifiable data or inability to extract sufficient data. This resulted in four studies with adequate data to be included in the meta-analysis (pooled $N = 60$ participants). In these studies, hair density was the measure of treatment success. The meta-analysis examined the standardized mean difference overall and for each of the four studies using a forest plot, taking into consideration heterogeneity as measured by the I^2 statistic. All analyses were conducted using RevMan 5 (Copenhagen, Denmark). All 13 human studies will be described qualitatively.

Results

In vitro *and murine model studies*

Two trials established positive results *in vitro* and in murine models. These trials confirmed that PRP induced a significant increase in the number of newly formed follicles as well as shortened the time of hair formation by two days (19). Near complete hair regrowth was observed in mice, while *in vitro*, both proliferation of DP cells and conversion of cells from telogen to anagen were increased (5).

Human studies: meta-analysis

Comparisons of PRP treatment with baseline were conducted in the four included studies (Figure 1) (11,20–22). The overall standardized mean difference was 0.51 [95% confidence interval (CI): 0.14, 0.88; $I^2 = 0\%$] in favour of PRP. All findings were in the same direction. These results suggest that PRP may be an effective treatment for AGA.

Human studies: qualitative descriptions

Thirteen articles were human studies. Of these, Uebel et al. used a slightly different approach in a trial of 20 patients that provided preliminary evidence to support the use of PRP in combination with hair transplantation in men (23).

The further 12 studies investigated the use of PRP injections directly into the scalp, with methods varying greatly. For instance, inclusion of leukocytes (24) and CD34 + (25,26) cells in PRP preparations was employed in an attempt to augment the treatment in three trials of 64, 26 and 40 patients, respectively. Use of PRP-containing leukocytes led to an increase in hair thickness and numbers compared to baseline, resulting in a clinically important difference in over 40% of patients; however, patients were evaluated through subjective investigator assessment, and no controls were employed (24). Likewise, use of CD34 + cell-containing PRP also led to a significant increase in hair thickness and numbers compared to baseline as measured through Follioscope PT® software (25).

Of the remaining nine human studies, only Borhan et al. mentioned about the use of a non-activated PRP treatment (20). A slight improvement in hair density was discussed; however, these results were not significant (Student's t test, $p > 0.05$), and controls were not used (20).

Comparatively, an increased efficacy was observed in many of the trials which employed activated (use of calcium chloride or similar aggregation inhibitor to induce release of growth factors from alpha granules) PRP (21,22,27,28) while efficacy was also reported in studies which do not mention either use or avoidance of activators (11,29–31). These studies included 140 patients where clinical and significant improvements in hair counts and density, thickness, root strength as well as a decrease in hair loss assessed mainly through physician, image and trichogram evaluation was observed (11,21,22,27–30). Microscopic evaluations showed a significant ($p < 0.05$) increase in epidermis thickness and number of follicles as well as cell proliferation measured through Ki67 evaluation in two trials (21,30). Similarly, a thickened epithelium and increased proliferation of collagen fibers and fibroblasts were observed in a third study (11). Improvements in hair pull tests were also reported in four trials (22,27–29). A case report composed of a single patient also mentions an increase in growth rate (31) while FGF-2-releasing dalteparin and protamine microparticles added to PRP facilitated hair growth further than PRP alone (11). Taken together, these results may suggest a positive impact of PRP on hair growth; however, the data are limited as three of the trials, accounting for over 50% of patients, lacked controls (22,28,29).

Patient satisfaction was evaluated in three studies. Results were a consistent 7 on a 10-point scale across all studies (22,28,29) suggesting a perceived value from the patient perspective.

Patients were treated and followed for three months (11,27–29), six months (31), one year (21,22) and two years (30). Thus results were visible by three months but few studies have evaluated their long-term duration. One study has recommended additional treatments by 12–16 months (30).

The overall treatment was well tolerated. Only minor side effects were reported including erythema, edema, headaches, drowsiness, mild pain, temporary swelling and scalp sensitivity (11,20–22,24,25,27–31).

Discussion

With the introduction of PRP therapy in the hair restoration field, multiple applications have been created. There is preliminary evidence that PRP could be used to increase the yield of follicular units in hair transplant surgery as well as multiple methods for the preparation of PRP for scalp injections in the treatment of AGA. As this field is still new, there are many variables to determine

such as whether PRP should be activated, which additional components are beneficial as well as the quantity and frequency of treatments required. Additionally it would be advantageous to establish a standardized and quantitative measure of treatment success to allow uniform comparisons across trials.

As there are many methods for the preparation of PRP, the most suitable for AGA therapy is not yet clear, although a few basics have been established. To isolate PRP, some laboratories use a single-spin method with success (22), however whether using a manual protocol or a commercial system, many use a double-spin method (32). Moreover, approximately 1–1.5 million platelets/μl is generally regarded as the therapeutically effective concentration, meaning platelets must be enriched 4–7 times that of baseline (33).

Once the PRP has been isolated, it must be activated to release the growth factors from alpha granules (34). Aggregation inhibitors such as thrombin and calcium chloride are commonly used (34) although Borhan et al. (20) argue that the preparation and injection process, including contact with dermal fibroblasts, should induce activation and therefore refrained from external activators. Meta-analysis results showed the standardized mean difference of this study (0.06; 95% CI:−0.61, 0.71) to be the lowest of the four compared. This study also had a wide confidence interval that spanned over 0, suggesting addition of activators may be beneficial although likely not the sole reason for these observations. For example, another obvious difference was time of treatment assessment as Borhan et al. (20) used a 16-week timeline versus the three months used in the remaining trials (11,21,22).

The literature also includes discussion of additional components believed to contribute to PRP's positive effects on hair growth. When isolating platelets, Schiavone et al. (24) retained leukocytes, arguing for their role in infection inhibition (35,36), immune regulation (37,38) and production of VEGF (39). Two studies mention CD34 + cells in addition to leukocytes due to their angiogenic potential (25,26). Takikawa et al. showed that inclusion of dalteparin and protamine microparticles for controlled release of growth factors led to increased hair growth compared to PRP treatments alone (11). This innovative expansion of basic PRP treatment seems promising; however, current knowledge is limited by a lack of controls in the leukocyte study (24) as well as an inability to compare findings due to diverse methods of treatment assessment.

Quantity and frequency of required treatments are also unclear. Study protocols included anywhere from one to five treatments spaced from a week to three months apart. Of the four studies which were compared through meta-analysis, the study with the largest standardized mean difference (0.78; 95% CI: 0.14, 1.43) used three treatments at 21-day interval (22) while the study with the lowest standardized mean difference (0.06; 95% CI: −0.61, 0.74) used four treatments with 3- and 6-week interval (20). Unfortunately, due to other key differences in methodology, (including activation) as discussed above, the effect of additional treatments is not obvious although current literature does concur that follow-up and continuing treatments are necessary to maintain maximum results. Schiavone et al. hypothesized the need for booster treatment at 10–12 months (24). After one year, with three treatments in the first three months and a booster treatment at six months, Gkini et al. observed maximum results at three months (22). The study of the longest duration followed patients for two years and began to observe relapse around 12 months after the last treatment (30). Therefore, patients will most likely require semi-regular treatments to prevent loss of new growth.

Taken together, these 12 studies, 4 of which produced moderate support for the effectiveness of PRP in AGA when combined in a meta-analysis, suggest the investigation of PRP treatment for AGA is worth pursuing. As there is so far an absence of adverse events, PRP has already become an attractive off-label treatment alternative. PRP provides an option for patients recalcitrant to the currently approved therapies minoxidil and finasteride. Moreover with the daily applications required for the proper use of minoxidil considered cumbersome, and growing concern over potential finasteride-induced side-effects, an additional treatment would be advantageous. Also worth note, patient satisfaction was almost identical when surveyed throughout three trials, suggesting that patients find the procedure beneficial (22,28,29).

It must be stated that the evidence to date is suggestive, not definitive. Clinical studies require the inclusion of more precise metrics to evaluate the efficacy of PRP therapy. To move the field forward, controlled trials using quantitative measures of treatment success reporting both measures of central tendency as well as statistical variability are required. In this present analysis, we found that hair density was a good candidate as a non-subjective, uniform measure for comparison across trials. Moreover with more refined data, it may be possible to better identify an ideal patient profile. For example, there is some evidence that neither age nor gender affects outcome (24,25). This is an important finding for women with AGA, as most current therapy is targeted towards men. Better results were observed, however, in those with less severe AGA (Norwood IV or less) as well as a shorter duration of AGA (2–4 years or less) (20,22,29), but not in all cases (24,25). More research to further define and confirm these observations is needed.

Overall, PRP is an innovative treatment that is quickly becoming popular in the field of hair restoration. Currently there is evidence to support its potential efficacy, however further investigation is required. New research will hopefully provide the data required to evaluate protocols for activation, additional beneficial components, and the minimum required frequency of treatments for effective results. The establishment of PRP as an approved therapy for AGA would be exciting progress in a field where current options are limited, (especially in the case of women) require time-consuming daily applications or elicit concern for serious side effects.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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