Evaluation of the effectiveness of androgenetic alopecia treatment in men using platelet-rich plasma: A systematic review of randomized, placebo-controlled trials

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Evaluation of the effectiveness of androgenetic alopecia treatment in men using platelet-rich plasma: A systematic review of randomized, placebo-controlled trials

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ABSTRACT:
Platelet-Rich Plasma becomes more and more popular treatment alternative or additional method in androgen alopecia (AGA). AGA is a multifactorial disease, in which testosterone plays a significant role in influencing hair growth.

The aim was to evaluate the effectiveness of PRP treatment in androgenetic alopecia affecting men. The research was performed using the following databases: PubMed, Embase, and Cochrane Library. The effects were measured with a Tricho-Scan and the measure of the effect was the difference between the initial and final hair density.

A significant difference was observed between the areas of the scalp where PRP injections were made and those where saline was administered. Compared to conventional minoxidil 5% topical platelet-rich plasma therapy PRP is more effective in male-pattern baldness treatment. A beneficial effect of combining PRP Therapy with minoxidil 5% was observed, therefore PRP is not only an excellent alternative for patients in whom the minoxidil 5% topical monotherapy did not bring the expected effect or experienced unacceptable side effects, but also can be used as a complementary therapy.

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INTRODUCTION:

Androgenic alopecia (AGA) affects about 50% of Caucasian men by 50 years of age and is characterized by progressive hair loss. Although it can affect both sexes, the clinical presentation differs in men and women. In men androgenic alopecia is usually seen in bilateral temporal and vertex areas. The main factor of this type of hair loss is a high level of androgen hormones. Dihydrotestosterone (later named DHT) is a metabolite of testosterone produced by 5-alpha-reductase. Type 2 of 5-alpha-reductase is found in the outer root sheath of hair follicles and is instrumental in AGA.[1] Androgen receptors (AR) have two domains - one responsible for binding a ligand (in this case androgen hormones) and the second DNA binding. Activation of the AR leads to exposure of androgen sensitive genes, including gene controlling hair growth cycle.[2]

Conventional treatment includes 5% topical minoxidil, 5-alpha-reductase inhibitors (finasteride), which prevent DTH production. Minoxidil administrated topically leads to vasodilation, angiogenesis and cell proliferation, but in some patients, it may cause contact dermatitis. Finasteride is a per os drug that inhibits type II 5-alpha-reductase, while Dutasteride inhibits both I and II type.[3] Usage of these drugs carries a certain risk of sexual dysfunction.[4] Off-label therapies include prostaglandins analogs, 2% ketoconazole shampoo, anti-androgens, laser treatment, surgical treatment (hair transplantation), and cell mediated treatment, which is the topic of this study.

The Platelet-Rich Plasma (PRP) is a blood-derivative, previously used in thrombocytopenia treatment.[5] With time, when the regeneration-stimulating effect of platelet-rich plasma was observed, it began to be used in many other fields of
medicine, including orthopedics, gynecology, dermatology, urology, and ophthalmology. [6]

To obtain PRP, citrated blood was used in the centrifugation process to prevent coagulation. The anticoagulant usage leads to liquid platelet-rich plasma obtaining otherwise, we would get a PRF [7] that has a different use and is not the subject of this study.

A high concentration of autologous platelets is present in a small quantity of plasma after centrifugation of the patient's blood. Alpha granules in the platelets promote stem cell regeneration and remodeling of soft tissue. There are many growth factors in alpha granules of thrombocytes, such as platelet-derived growth factors (PDGF), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), transforming growth factor-beta (TGF beta), and insulin-like growth factor (IGF).[8] The mitogenesis and differentiation of monocytes, fibroblasts, stem cells, keratinocytes, and endothelial cells occurs due to growth factors in the PRP alpha granule.[9]

MATERIALS AND METHODS:

**PICO:**

A systematic review was conducted according to the PICOS criteria and PRISMA protocol.

**Patient (P):** Men in all the stages of androgenic alopecia based on the Norwood scale

**Intervention (I):** Platelet Rich Plasma subcutaneous scalp injections

**Control (C):** Compared with placebo

**Outcome of interest (O):** Male pattern hair loss

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Focused question:

Search strategy
The reviewer performed computerized, systematic research using the following databases:
PubMed, EMBASE, and Cochrane Library using the following BOOLEAN operators:
"Platelet AND Rich AND Plasma" OR "androgen AND alopecia" OR "androgen AND hair loss" OR "PRP AND treatment" OR "treatment AND androgenic AND alopecia" OR "Platelet AND Rich AND Plasma AND injections" OR "baldness" OR "male AND pattern AND hair AND loss"

Study selection:
The investigator performed quality control of pre-qualified studies using the inclusion and exclusion criteria. The risk of bias was assessed as low based on a common classification scheme for bias.

The study could be included if it met the following inclusion criteria: male sex, hair loss clinically typical for androgen alopecia, randomized clinical trial with placebo control

Exclusion criteria: meta-analysis, systematic reviews, case reports, in vitro studies, animal experiments, lack of negative control

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Table 1. Characteristics of the studies

<table>
<thead>
<tr>
<th>Author</th>
<th>number of patients</th>
<th>outcome measure</th>
<th>treatment protocol</th>
<th>evaluation of the effect compared to control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro J et al. [12]</td>
<td>35</td>
<td>Hair density</td>
<td>3 monthly treatment sessions with evaluation after 3 months after the final treatment</td>
<td>No difference between study group and control group</td>
</tr>
<tr>
<td>Sultana BB et al. [18]</td>
<td>54</td>
<td>Hair density</td>
<td>3 sessions with 4 weeks intervals</td>
<td>Positive</td>
</tr>
<tr>
<td>Gentile P et al. [16]</td>
<td>23</td>
<td>Hair density</td>
<td>3 sessions with 30-day intervals, final evaluation 3 months after the last treatment</td>
<td>positive</td>
</tr>
<tr>
<td>Alves R et al. [15]</td>
<td>25</td>
<td>Hair density, mean anagen hairs</td>
<td>3 sessions with 30-day intervals</td>
<td>positive</td>
</tr>
<tr>
<td>Cervelli V et al. [14]</td>
<td>10</td>
<td>hair density, anagen/telogen ratio</td>
<td>evaluation after 14 weeks, 6 months and 12 months</td>
<td>positive</td>
</tr>
<tr>
<td>Pakhomova E et al. [19]</td>
<td>69</td>
<td>hair density</td>
<td>4 procedures with 1 month intervals</td>
<td>positive</td>
</tr>
<tr>
<td>Gentile P et al. [13]</td>
<td>23</td>
<td>residual hair count and hair density based on computerized trichogram</td>
<td>3 sessions with 30-day intervals, final evaluation after 2 years</td>
<td>positive</td>
</tr>
</tbody>
</table>
RESULTS

A total of 345 patients were selected for the study. The number of procedures ranged from 1 to 5 (mean=3; median=3) and the duration of the studies ranged from 2 months up to 24 months (mean=7 months; median=5 months).

The heterogeneity of the studies was mainly related to the different number of patients, the different duration of the study, the number of procedures performed and the length of the intervals, the different ages of the participants, the severity of the disease and whether minoxidil was used.

The outcomes of the studies were measured by TrichoScan, which is a digital software-supported epiluminescence technique for measuring hair count (number of hairs/0.65 cm2), hair density (number of hairs/cm2), hair diameter, anagen/telogen ratio, and vellus hair/terminal hair ratio.

6 studies included in this publication compared PRP injections with saline injections as a control group and 3 studies compared PRP treatment with 5% topical minoxidil treatment.

Table 1. Characteristics of the studies

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</tr>
</thead>
<tbody>
<tr>
<td>Singh SK et al. [20]</td>
<td>80</td>
<td>hair density, patient self-assessment, photographies</td>
<td>3 sessions with 1 month intervals and final evaluation after 2 months</td>
<td>positive</td>
</tr>
<tr>
<td>Takikawa M et al.[17]</td>
<td>26</td>
<td>Hair density, hair cross section,</td>
<td>5 sessions with 2-3-week intervals</td>
<td>positive</td>
</tr>
</tbody>
</table>
Table 2. Comparison of therapy effects in terms of hair density

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial hair density</th>
<th>final hair density in study group</th>
<th>final hair density in control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB Sultana.; PH Kumar [18]</td>
<td>15.41±1.16 and 15.56±1.88 hairs/sq.cm</td>
<td>19.14±1.06 hairs/sq.cm</td>
<td>17.62±2.07 hairs/sq.cm</td>
</tr>
</tbody>
</table>
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</tr>
</thead>
<tbody>
<tr>
<td>Gentile P.; Garcia-Garcovich S.; Scioli M.G. et al. [16]</td>
<td>225±15 and 218±17 hairs/sq.cm</td>
<td>282±20 hairs/sq.cm</td>
<td>227±16 hairs/sq.cm</td>
</tr>
<tr>
<td>R Alves, R Grimalt [15]</td>
<td>167.8 6±51.2 hairs/sq.cm</td>
<td>179.9 6±62.7 hairs/sq.cm</td>
<td>165.7 6±55.2 hairs/sq.cm</td>
</tr>
<tr>
<td>V Cervelli, S Garcia-Garcovich, A Bielli et al. [14]</td>
<td>159.4±47.6 hairs/sq.cm</td>
<td>187.1±52.5 hairs/sq.cm</td>
<td>168.1±43.3 hairs/sq.cm</td>
</tr>
<tr>
<td>EE Pakhomova, IO Smirnova [19]</td>
<td>408.4±43.6 hairs/sq.cm</td>
<td>539.6±52.1 hairs/sq.cm</td>
<td>554.8±53.5 hairs/sq.cm</td>
</tr>
<tr>
<td>P Gentile, S Garcia-Garcovich, A Bielli et al. [13]</td>
<td>161.2±41.9 hairs/sq.cm</td>
<td>207.1±56.3 hairs/sq.cm</td>
<td>170.3±42.1 hairs/sq.cm</td>
</tr>
<tr>
<td>SK Singh, V Kumar, T Rai [20]</td>
<td>90±41 hairs/sq.cm</td>
<td>143.20±33.35 hairs/sq.cm</td>
<td>123.95±35.41 hairs/sq.cm</td>
</tr>
<tr>
<td>Takikawa M et al. [17]</td>
<td>112±6 and 104±6 hairs/sq.cm</td>
<td>127±6 hairs/sq.cm</td>
<td>106±6 hairs/sq.cm</td>
</tr>
<tr>
<td>Shapiro J.; Ho A.; Sukhdeo K et al. [12]</td>
<td>151±39,82 hairs/sq.cm</td>
<td>170.96±37.14 hairs/cm²</td>
<td>166.72±37.13 hairs/cm²</td>
</tr>
</tbody>
</table>
DISCUSSION

Platelet-Rich Plasma injections are becoming a more and more popular alternative for conventional treatment of androgenic alopecia in men. The increasing popularity is due to, among others absence of a recovery period, safety, and good results. [10] Despite many studies, the mechanism of action and effectiveness remain unclear. It has been proved that platelet-rich plasma promotes proliferation of dermal papilla (DP) cells, but the intensity of proliferation did not correlate with increasing concentration of thrombocytes. [11]

Our team decided to assess the reliability and statistical validity of publications that met the inclusion criteria to be able to answer the questions about the effectiveness and safety of PRP as an alternative treatment for male pattern baldness.

The study by Jerry Shapiro et al. revealed no significant difference between the two groups, but hair density was significantly increased in both groups at the end of the studies compared to the baseline, which may indicate a remarkable role of the injections of the scalp alone. [12]

However, the other studies showed a significant difference between the study group and the control. In the study by Gentile P.et al. hair density in study group increased significantly (31%), while in the control group insignificantly (2%). [13]

The study by V. Cervelli as well as the study by P. Gentile and the study conducted by Rubina Alves and Ramon Grimalt even showed a decrease in hair density in the control group, which may be due to the method of administration of the saline solution. [14-16]

In the study conducted by M. Takikawa et al. impact of dalteparin and protamine microparticles (PRP&D/P MPs) on PRP was checked. Half of the patients received plain PRP injections on one side of the scalp, while saline was administrated on the
placebo side and the other half of the patients received PRP&D/P MPs instead of PRP on the same terms. In both groups difference between the placebo side and baseline was insignificant and in the study side the increase in hair density and cross-section was significantly higher than on the control side (p<0.01). Deterioration was not observed in any patient’s study side. The study revealed that PRP&D/P MPs addition brings better results and PRP alone, but the impact of PRP&D/P MPs alone remains unknown, thus further studies are needed. [17]

In a study by Sultana B. B. et al., PRP injections were compared with topical minoxidil 5% therapy. The effects indicate that plasma therapy brings better results. [18] However, we do not know to what extent this is due to the high concentration of platelets, and to which the injection procedure itself. To unequivocally determine which therapy brings the most beneficial effects, a study should be carried out in which the control group, in addition to minoxidil 5%, will also receive injections of saline.

Elena E. Pakhmova with the team took it a step further and, beyond the minoxidil 5% group and the PRP injection group, opened up a combination therapy group consisting of topical minoxidil 5% and PRP. The result of the study is consistent with the result of the study by Sultana B. B. et al., However in this case, it has been proven that the combination therapy brings the optimal effect. The use of minoxidil does not exclude the use of platelet-rich plasma, as these are methods with completely different target points. [19]

In a study by Satyendra Kumar Singh et al. the patients were divided into four groups, three of which were the same as in the study by E.E. Pakhmova, and the fourth group only received saline injections. In the case of the last group, a decrease in the hair density was observed after 5 months. The other results were consistent with the results of studies by E.E. Pakhmova et al. and Sultan B.B. et al., because
also in this case it turned out that the combination therapy brings the best effect, while the use of PRP alone is more effective than the topical application of minoxidil 5%. [20]

As previously mentioned, the injection method itself can have a significant impact on the final effect, both in the test group and in the placebo, but due to the differences between the groups, it should be assumed that the substances present in PRP have a great influence on the final effect.

Since some control groups experienced a significant or slight increase in hair density, while others showed a decrease in hair density, it may be assumed that the injection method, including the amount of bleeding during the procedure, contributed to the variability of the results.

Most of the studies involved a half-injection of the scalp with platelet-rich plasma, while the other half of the scalp was injected with saline. Therefore, the influence of growth factors present in PRP on the effect observed in control areas cannot be ruled out.

CONCLUSION

Summarizing the study, the following conclusions should be distinguished:

Platelet-rich plasma is an effective method in the treatment of androgenetic alopecia in men.

Platelet-rich plasma components increase hair density.

The use of combination therapy consisting of topically administered minoxidil 5% and at least 3 PRP injection sessions has a more favorable effect than either of these methods used in monotherapy.

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Platelet-rich plasma is a good alternative for patients in whom treatment with topical minoxidil did not bring the desired effect or experienced unacceptable side effects.

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**Authorship Statement:**

Julia Maria Borowiecka

Łukasz Pałka, Ph.D.

**CRediT statement:**

J.M. Borowiecka: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - Original Draft

Ł. Pałka, Ph.D.: Validation, Resources, Writing - Review & Editing, Supervision

**REFERENCES**


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