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COMPARISON BETWEEN PLATELET-RICH PLASMA SINGLE- AND DOUBLE-SPIN CENTRIFUGATION TO TREAT ANDROGENETIC ALOPECIA: A SYSTEMATIC REVIEW

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Abstract

There are no established guidelines for the management of androgenetic alopecia (AGA). A new therapy with promising results is Platelet-Rich Plasma (PRP). PRP has a variety of preparation methods, such as single spin and double spin centrifugation and still there is no consensus on the method of preparation. There is controversy of which preparation method is better. We searched PubMed, EBSCO, Clinical Key, ProQuest, Cochrane Library, Science Direct, Clinical Trial, Open Access, Wolters Kluwer, Google Scholar, GARUDA, and AtmaLib until Oct 2020 for human studies using PRP for AGA treatment. We assessed 3375 papers; 6 studies met the inclusion criteria and evaluated 128 AGA patients, 112 male and 16 female, 18-63 years old. Participants varied from type II-VI based on the Hamilton-Norwood classification system and degree 2 based on the Ludwig classification system. Four studies used the single-spin centrifugation PRP preparation method and two studies used the double-spin PRP preparation method. The studies stated the increases in growth factor levels. All studies showed PRP significantly affected hair growth in AGA patients. PRP has been shown to increase hair growth parameters in form of hair density (P <0.0001). PRP has been shown to increase hair density and hair count. Growth factors in PRP induce cell proliferation and tissue angiogenesis. The results of single-spin centrifugation preparation method provide a greater increase in hair density. But, data reports from the study did not allow comparisons to determine the best PRP preparation method for AGA treatment. Therefore further study is needed.

Keywords: *Alopecia Androgenetic, Growth Factors, Hair Density, Platelet-Rich Plasma*.

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Introduction

Alopecia occurs in large population of men and approximately 30% of women during their lifetime (Puspitasari et al., 2019). The most common type of alopecia is androgenetic alopecia (AGA) with prevalence of 90% of all alopecias (Ho et al., 2017). Drugs approved by the Food and Drug Administration (FDA) in treating AGA are minoxidil and finasteride (Kanti et al., 2018). In some cases, minoxidil can cause tachycardia, dizziness, swelling, weight gain, hypertrichosis, fainting, chest pain, contact dermatitis, and hirsutism. Meanwhile, finasteride can cause sexual dysfunction (McClellan & Markham, 1999). Drug administration and schedule affect medication adherence rates. Many AGA patients skip to take medication so the recovery is hard to achieve.

To date, no guidelines that has been established for AGA (Lucky et al., 2004). Research on a new modality that shows promising results as AGA therapy is Platelet-Rich Plasma (PRP) (Verma et al., 2019). In journal on molecular science, Gentile stated that PRP autologous can treat AGA and no side effects have been recorded (Gentile et al., 2015). PRP was chosen based on its effectiveness and success rate in AGA therapy compared to other modalities (McElwee & Shapiro, 2012). Use of PRP for the management of alopecia is more beneficial than Platelet-Rich Fibrin (PRF) because it releases more alpha granules that contain growth factors (Ehrenfest et al., 2009). PRP is more widely use rather than laser light therapy because lasers tend to produce ineffective and consistent results, can interact with other drugs, only works in some patients, and is very expensive (Abella et al., 2022). PRP is given in one-cycle, three times in 3-4 months and results can be seen in 3-4 months, quicker and more certain than minoxidil that needs for 6-12 months if used regularly every day.

So far, there has been no settlement of preparation method for administering PRP as therapy of AGA (Dhurat & Sukesh, 2014). Various studies on PRP include different methods, either single-spin or double-spin of centrifugation (Ayatollahi, Hosseini, Shahdi, et al., 2017). Some studies say single-spin process is better, but other studies say double-spin process is better (Pakhomova & Smirnova, 2020). This topic is concerned because theory said that preparation method will affect the PRP product by its bioactive materials, such as growth factor. The comparison of single-spin and double-spin centrifugation of PRP as AGA therapy is still questionable. If it is difference, it results different PRP products too. In this systematic review, researcher interested in knowing the comparison of PRP administration with single-spin and double-spin centrifugation and which preparation method is better for treatment of AGA.

Research Methods

This is a systematic review to see the comparison of PRP administration with single-spin or double-spin centrifugation as preparation method on growth factors and hair growth parameters of AGA patients.

A. Search Strategy

Systematic literature study search carried out by two authors in *PubMed, EBSCO, Clinical Key, Proquest, Cochrane Library, ScienceDirect, Clinical Trial, Open Access, Wolter Kluwer, Google Scholar, GARUDA.* Grey literature sought from university libryary, AtmaLib. Hand searching is done on Google search engine and the articles referred to journal from databases.

Keywords *used* to find independent variable were "*Platelet-Rich Plasma"*, "*Platelet Concentrate*", and in Indonesian "Konsrentrat Platelet", "Plasma Kaya Trombosit", "Plasma Kaya Platelet". To search the dependent variable, the keywords were "*Alopecia*", "*Alopecia Androgenic*", "*Alopecia Androgenetic*", "*Pattern Baldness*", "*Pattern Hair Loss*", "*Baldness*", "*Growth Factor*", and in Indonesian "Alopesia", "Alopesia Androgenik", "Alopesia Androgenetik", "Konsentrat Platelet", "Kebotakan", "Faktor Pertumbuhan". Variabels were connected by "and" or "*dan*", meanwhile the same variable were connected by "or" or "*atau*". To comprehend related articles, we searched ("*Platelet-Rich Plasma*" OR "*Platelet Concentrate*") AND ("*Alopecia*" OR "*Alopecia Androgenic*" OR "*Alopecia Androgenetic*" OR "*Pattern Baldness*" OR "*Pattern Hair Loss*" OR "*Baldness*") OR ("*Growth Factor*"). There is no language restriction applied for identifying the literatures. Studies found by two authors were managed by Zotero as bibliographic management and elimination of duplication was also carried out with Zotero.

B. Study Selection

Study selection based on PICOS (Patient, Intervention, Comparison, and Outcome). PICOS in this *systematic* review are AGA patients, the intervention is the administration of single-spin centrifugation PRP, the comparison is the administration of double-spin centrifugation, outcomes evaluated by hair growth parameters (i.e. hair density, hair count and hair diameter) and the study design is experiments in human. The identified papers were experimental study in human that evaluate PRP administrations for AGA treatment in terms of hair density and growth factors. The excluded papers were studies that did not provide clarity of data for processing, studies without full text available and studies with Hamilton-Norwood classification system or Ludwig classification system to evaluate hair growth. Two authors review the studies separately and discussed to decide which studies need the requirements.

C. Data Extraction

The data collected from journals were extracted by two authors and one coauthors. Differences in opinions were resolved by consensus. The data included authors, journals, number of samples, characteristics of patients (gender, age and AGA type), research methods, PRP preparation methods, and study evaluation result (growth factors and hair growth parameters, i.e. hair density, hair count or hair diameter).

Results and Discussion

The searching process found 3375 papers from databases. Number of 573 duplications were eliminated leaving 2802 papers. A total of 2793 paperes did not meet

the inclusion criteria and resulted 9 papers. Of the papers, 3 studies did not accommodate complete manuscripts so total of 6 papers were assessed using the RoB (Risk of Bias) quality assessment tools. The PRISMA diagram of this research flow is shown in Figure 1. Below. The result

Figure 1. PRISMA Diagram.

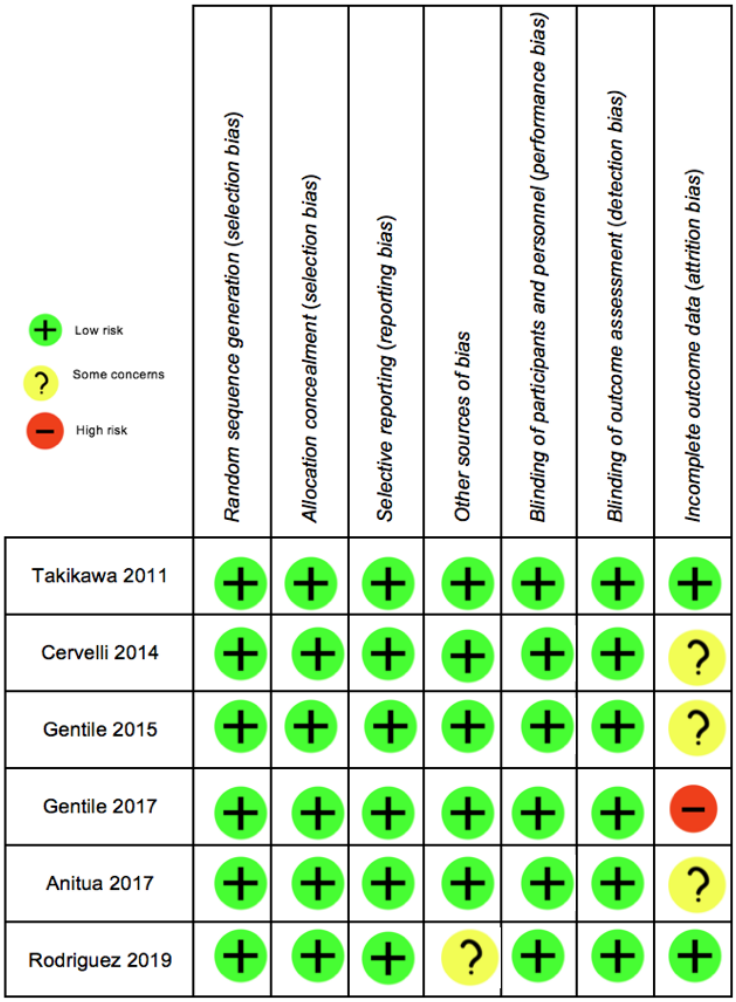

Figure 2. Quality Assessment with Risk of Bias (RoB) Cochrane Collaboration.

The six selected studies took place in 2011-2019. Three articles were randomized controlled trials and three articles were clinical controlled trials (Gentile et al., 2017). Total participants of this six studies are 128, consists of 112 men and 16 women by age range 18-63 years old. AGA type are varies from type II-VI based on the Hamilton-Norwood classification system and degree 2 based on the Ludwig classification system. all the six studies concluded that PRP affects hair growth (Rodrigues et al., 2019). All of six papers measured the growth factors and hair growth parameters, including hair density and hair count. Characteristics of studies are shown in **Table 1.** below.

A. Growth Factors

Four studies stated an increase of growth factors level in PRP by each paper's preparation methods of PRP. Two studies did not mention the exact growth factors level, but the reference journal regarding the protocol oh preparation method it used indicated an increase levels of growth factor (Castillo et al., 2011). One study did not write the number of growth factors level, on the other hand just served the increases on tables and charts of ranges.

B. Hair Growth Parameters

The six studies stated that there were differences in hair density before and after PRP injection in AGA patients. There were four studies that measured hair counts and their mean increases compared to placebo. Four studies also used histomorphometric analysis and measured follicle counts as well as levels of Ki67, which there were increases of levels (Anitua et al., 2017). One study measured CD31 and the results increased. Result studies are presented in **Table 2.** below.

Table 1
Characteristics of Studies.

Study	Patient (Age)	Inclusion Criteria	Intervention	Control Group	Administration	Injection	Injection Area	Preparation Methods	Follow-up
Takikawa et al 2011[127]	26, 16 males, 10 females (28-59 years old)	Patient with thin hair in frontal and parietal area	PRP double-spin process	Saline	5 injections, week 0, 2, 4, 6, 9	3 ml	Bald area for PRP, opposite area for control	15 ml of blood is centrifuged, first spin 15 minutes 1700 rpm, second spin 5 minutes 300 rpm	Before intervention (baseline), 12 weeks after injection
Cervelli et al 2014[128]	10 males (22-60 years old)	AGA patient type IIA-III in frontal, parietal, or vertex area	PRP single-spin process	Saline	3 injections, week 0, 4, 8	9 ml	AGA frontal and parietal injected in frontal, control in parietal and AGA parietal and vertex, injection in parietal, control in vertex	*Cascade-Selphyl-Esforax system* 18 ml of blood centrifuge 10 minutes 1100 rpm	T0 beginning of study, T1 after 2 weeks, T2 after 6 months, T3 after 1 year

Gentile et al 2015[23]	23 males (19-63 years old)	MPHL type IIA-IV	PRP single-spin process	Saline	3 injections, interval of each injection are 30 days	9 ml	AGA frontal and parietal injected in frontal, control in parietal and AGA parietal and vertex, injection in parietal, control in vertex	*Cascade-Selphyl-Esforax system* 60 ml of blood is centrifuge 10 minutes 1200 rpm	Before intervention, 2 months after injection
Gentile et al 2017[129]	24 males (19-63 years old)	MPHL type IIA-IV	PRP single-spin process	Saline	3 injections with interval of each is 30 days	0,2 ml/cm^2	Bald area for PRP, opposite area for control	*CPunT preparation system* 55 ml of blood centrifuged 10 minutes 1200 rpm	Before intervention (baseline), 12 weeks after injections

Study	Patient (Age)	Inclusion Criteria	Intervention	Control Group	Administration	Injec-tion	Injection Area	Preparation Methods	Follow-up
Anitua et al 2017[130]	19, 13 males, 6 females (19-63 years old)	MPHL class III-VI, FPHL type 2	PRP double-spin process	Saline	5 injections, 1st, 2nd, 3rd, 4th, 7th month	3-4 cm^3	Area with thin hair	18 ml of blood centrifuged, first spin 8 minutes 2000 rpm, second spin 10 minutes 2800 rpm	Before intervention (baseline), 1 year after injection
Rodrigues et al 2019[131]	26 males (18-50 years old)	Presentation of AGA III *vertex*	PRP single-spin process	Saline	4 injections with 15 days interval	Not discussed	Bald area for PRP	51 ml of blood centrifuged 10 minutes 2800 rpm	Before intervention, 15 days after, and 3 months after injections

Table 2
Summary of Result Studies.

Outcomes **Sample**	**Study**	**Result**	**GRADE**	**What Happens**
Growth factors level AGA Patient: 128 people (18-63 years old) Follow-up:	Takikawa et al 2011[127]	PDGF 331,8 ± 92,5 ng/ml TGFβ 1,4 ± 0,1 ng/ml VEGF 312,2 ± 43,9 pg/ml EGF 32,2 ± 3,6 pg/ml FGF 14,4 ± 2,9 ng/ml IGF-1 1,2 ± 0,1 ng/ml	++++ *High*	There is 31-100% growh factors concentrated in PRP

PRP product from centrifugation (6 studies) P < 0,001 – 0,05 (6 studies)	Cervelli et al 2014[128]	PDGF 14,8 ± 2,5 ng/mL TGFβ 0,1 ± 0,008 ng/mL VEGF 0,3 ± 0,3 ng/mL	+++ *Moderate* *Due to risk of bias*	Growth factors level is higher rather that in normal blood plasma
	Gentile et al 2015[23]	PDGF 14,8 ± 2,5 ng/mL TGFβ 0,1 ± 0,008 ng/mL VEGF 0,3 ± 0,3 ng/mL	+++ *Moderate* *Due to risk of bias*	Growth factors level is higher rather that in normal blood plasma
	Gentile et al 2017[129]	Counted PDGF, VEGF, IGF-1, TGFβ, but not stated the exact number	++ *Low* *Due to Indirectness and publication bias*	There is increases of growth factors level in PRP

Outcomes **Sample**	**Study**	**Result**	**GRADE**	**What Happens**
	Anitua et al 2017[130]	PDGF 21 ± 12 ng/ml TGFβ 33 ± 10 ng/ml VEGF 218 ± 127 pg/ml EGF 862 ± 221 pg/ml Trombospondin 1 268 ± 58 Angiopoietin 1 392 ± 122 μl/ml	+++ *Moderate* *Due to risk of bias*	Growth factors level is higher rather that in normal blood plasma
	Rodrigues et al 2019[131]	Counted PDGF, EGF, but just showed graphic of ranges	+++ *Moderate* *Due to publication bias*	PDGF and EGF showed correlation with platelet counts

Outcomes **Sample**	**Study**	**Parameter(s)**	**Result**		**GRADE***	**What Happens**
			Placebo	**PRP**		
Hair Growth Parameters AGA Patients: 128 people (18-63 years old) Follow-up: Before injections until one year after injections (6 studies) P < 0,0001 – 0,05 (6 studies)	Takikawa et al 2011[127]	Hair count Hair Density	1,9% 1,8%	13,4% 18,3%	++++ *High*	PRP group has higher hair density than control group (P < 0,01). There are thickening of epithelial and proliferation of fibre, collagen and blood vessels.
	Cervelli et al 2014[128]	Hair count Hair density Histomorpho-metric evaluation	2 3	18 27,7 Follicels, Ki67	+++ *Moderate* *Due to risk of bias*	PRP group has higher hair density than control group (P < 0,0001). There are thickening of epidermal layer and Ki67 (P < 0,05).

Outcomes **Sample**	**Study**	**Parameter(s)**	**Result**	**GRADE**	**What Happens**	***Outcomes*** **Sample**
	Gentile et al 2015[23]	Hair density Histologic evaluation Immunohisto-chemistry	3,2 3,8	33,6 45,9 Follicles, Ki67	+++ *Moderate* *Due to risk of bias*	PRP group has higher hair density than control group (P < 0,0001). There are thickening of epidermal layer and Ki67 (P < 0,05).
	Gentile et al 2017[129]	Hair density Hair count	< 1% 1,1 ± 1	31% ± 2%	++ *Low*	There is increasing of hair count in PRP non-activated group

		Histologic evaluation	↑36 ± 3 Follicles, Ki67↑, CD 31 ↑	*Due to Indirectness and publication bias*	than control group (P < 0,0001). There are increasing of Ki67 (P < 0,05) and CD31 (P < 0,01).
	Anitua et al 2017[130]	Hair density Hair diameter Histologic evaluation	↑39 ± 7 ↑18 ± 1 Follicles, Ki67↑	+++ *Moderate* *Due to risk of bias*	There is increasing of hair density in PRP group (P < 0,05). There is increasing of Ki67 in PRP group (P < 0,05).
	Rodrigues et al 2019[131]	Hair density Hair count	↑ ↑	+++ *Moderate* *Due to publication bias*	There is increasing of hair density (P < 0,012) and hair count (P < 0,016) in PRP than control group.

*GRADE (Grading of Recommendations, Assessment, Development and Evaluations)

High : true effect is similar to the estimated effect

Moderate : true effect is probably close to the estimated effect

Low : true effect might be markedly different from the estimated effect

Very low : true effect is probably markedly different from the estimated effect

Discussion

PRP is first generation platelet concentrate produced by autologous blood centrifugation. PRP contains platelets 5-9 times higher than normal platelets in the blood. There are alpha granules in platelets that store bioactive materials, for example growth factors, such as PDGF, TGFβ, VEGF, EGF, FGF, and IGF-1. Growth factors play a role in increasing cell proliferation, differentiation, and tissue angiogenesis. Using PRP as treatment for AGA patients causes hair regrowth and thickens the hair strands. The growth factor activates follicle cells on hair root bulb and prolongs the anagen phase of hair growth so that hair that was previously miniaturized will grow back to its size. The lifespan of the improved strands will also return to normal as the tissue cascade signal is reactivated by growth factors attached to receptors around the hair roots (Lekovic et al., 2002).

This systematic review discusses six studies related to PRP as the management of AGA evaluated from hair growth parameters in the form of hair density and the number of growth factors (Gentile et al., 2015).

Hair density, number of hairs in a defined area of 1 cm^2 on the six papers showed an increase from before the injection treatment with PRP (Gentile et al., 2015). This results are in line with the theory about administration of PRP that rich in growth factors will result in better hair growth in AGA patients. After PRP injection that is rich in growth factor, fibrin architecture is formed from platelets in the epidermal area of hair follicle cells. Platelets will release many growth factors. The results of the reaction and the action of growth factors are evidenced by a significant increase in the epidermal layer, an increase in hair density, and an increase in the number of hair counts in the area given the PRP injection (Chahla et al., 2017).

Histomorphometric analysis reported there are increases proliferation in epidermal cells and hair root follicles. the active role of bioactive molecules present in PRP can be interpreted from hair growth parameters. The role of growth factors is associated with the mitogenesis of thinned papillae cells on AGA, so that after therapy an increase in the epidermal layer is obtained. Growth factors that enhance mitotic activities have been shown to be associated with the regulation of extracellular kinase signals or the Akt activation pathway. The increases in CD31 and Ki67 cells indicates that active cells are dividing and associated with increased cell growth. In addition, growth factors can activate Bcl-2, protein that can prevent cell death and thus promote better quality of hair growth (Ayatollahi, Hosseini, Gholami, et al., 2017).

Another role of growth factor is to reduce inflammation around capillary blood vessels of hair follicles. The reduced inflammation is associated with attenuation of the nuclear factor of kappa pathway. histology findings show an increase in plexus of blood vessels around hair root follicles. this is associated with the release of growth factors VEGF, FGF, and IGF-1 from alpha platelet granules. VEGF plays a role in mediating the angiogenesis. Role of PDGF and EGF lies in binding with undifferentiated cell receptors in hair root on bulbous area. the bonds form a proper growth area or niche for cell

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differentiation into new bulbous hair follicles. cell activation and angiogenesis mutually support the enhancement of new hair growth in AGA patients. High level of growth factors in PRP affects hair growth in AGA patients. Researchers suggest connection related to increasing of Wnt signals regulation and growth factor overexpression.

Growth factor and hair growth parameters in the form of hair density are closely related to each other because hair density shows quantitative evidence of the work mechanism and benefits of growth factors. Since a higher number of growth factors is better to enhance hair growth, PRP with preparation method that produces higher number of platelets will be better to apply. Preparation methods of PRP has not been settled and has great diversity. PRP can be produced by manual preparation methods by single-spin or double-spin centrifugation, but there are also commercially available kits of PRP (Etulain, 2018).

Data from six papers reviewed did not explain the details of each PRP preparation methods. This occurs is the effect of no protocol of PRP preparation method that has been decided globally. Therefore, each study can use of modify the existing preparation method according to their own tools, availability, and facilities. Total of four studies used single-spin centrifugation process and two studies used single-spin centrifugation process. The two studies that adopted the same preparation method did not even have the same centrifugation speed because one study modified the speed.

From many articles evaluating PRP benefits on AGA, the preparation methods of each paper varies widely. The selection of six studies in this systematic review included the requirements for immunohistochemistry measurements of hair growth factors and hair density. However, not all six papers assessed result under the exactly same criteria. Research about PRP preparation method mostly does not fully explain its details. The preparation methods in this six studies also describe the process of producing PRP, but they are not complete enough to be paralleled to one another. The result of comparing this data, four studies that using single-spin centrifugation recorded a greater increase in hair density and growth factors rather that the double-spin centrifugation. However, this statement must be proven objectively by means of systematic calculation or meta analysis in research with detailed preparation methods. Two studies that has been assessed also did not calculate the total of growth factor directly so that comparisons between single- or double-spin centrifugation of preparation method and its correlation to hair density and growth factor could not be aligned comprehensively.

Conclusion

PRP has been shown to increase hair growth parameters in the form of hair density. The work mechanism of PRP using high levels of growth factors to induce cell proliferation and tissue angiogenesis. Hair root follicles undergo cell regeneration so that new hair that grows will reach over the scalp. This proves that growth factors affect therapy of AGA.

There is significant difference in PRP administration with different preparation methods between single-spin and double-spin centrifugation. The amount of growth

factor in PRP is associated with increase of hair density, PRP with preparation method that results in more levels of growth factors can provide better hair growth results. The results of single-spin centrifugation preparation method gave greater increase in hair density. Besides that, the protocol for preparation method for each study is different, so more systematic test is needed to obtain more objective and accountable quantitative data. Reporting data from studies does not allow comparisons to determine the best PRP preparation method for AGA treatment due to the diversity of studies, protocols, and variables used. Not enough data, inequality of reported variables and lack of protocols completeness is a form of inconsistency in the study so the best preparation method can not be concluded.

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