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Original Article

The effectivity of platelet rich plasma on melasma: A systematic review and meta-analysis

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Abstract

Background Melasma is an acquired hyperpigmentation in the form light brown to dark brown macules on areas exposed to Ultraviolet (UV). Melasma accounts for 50% of aesthetic cases in Asia. Therapy of melasma depends on the type of melasma, the effectiveness of previous therapies, and the patient's expectations. Difficult in the management of melasma are frequent recalcitrant, tendency of recurrence, risk of side effects, long treatment and patient compliance. The latest therapy that is being used is Platelet rich plasma (PRP) containing TGF-β1 which significantly suppresses melanin synthesis, thereby lowering the mMASI score of melasma patients.

Methods Searching the electronic database Medline Pubmed, Scopus, EBSCOhost, ProQuest, Cochrane library, ClinicalTrials.gov, found 5 articles included in the qualitative (n=154 subjects) and 4 articles (n=103 subjects) included in the meta-analysis.

Results The mean difference in mMASI scores before treatment in the PRP injection treatment group and the control group was negative. This value indicates a decrease in the mMASI score after PRP injection. The control group also showed the same thing. The greatest decrease in mMASI scores in the study by Gamea, 2020 with PRP injection and topical tranexamic acid treatment was -8.5±2.76, the smallest in the study by Sirithanabadeekul, 2019 in the control group receiving normal saline injection, which was -1.42±0.93. The heterogeneity test results showed Q value = 24,564, df = 3; p<0.001, I2= 87.787. The I2 test outcome with p<0.001 showed that the data were homogeneous. The meta-analysis results present the Q statistic value was z= -5.373 (p=<0.001). This shows that overall offering PRP can significantly reduce the mMASI score.

Conclusion The implemented meta-analysis and systematic results show those who were given PRP intradermal injection therapy there was a decrease in mMASI scores that had occurred before treatment. The decrease in mMASI scores in the group given platelet rich plasma was lower than the control group given tranexamic acid injection in melasma patients.

Key words
Platelet rich plasma, melasma, mMASI, tranexamid acid.

Introduction

Melasma is a symmetrical acquired hyperpigmentation in the form of light to dark brown patches on areas exposed to sunlight (ultraviolet light), most commonly on the face. Melasma often occurs in Fitzpatrick skin types III to V who live in areas with high ultraviolet light intensity.[1-3] Melasma is reported to affect 9% of the Hispanic population in the southern United States to 40% in Southeast Asia.[1,2] Melasma accounts for 50% of aesthetic cases in

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Asia.[4] Melasma can be found in both women and men.[5]

The pathogenesis of melasma is still unclear. The main predisposing factors include genetics, ultraviolet exposure, and hormonal, cosmetic, drug and idiopathic.[3,6] The clinical features of melasma are brown to dark brown macules, irregular borders, symmetrical, along the forehead, temples, upper lip, cheeks, and other areas exposed to UV light.[1,6,7] The choice of melasma therapy depends on the type of melasma, the effectiveness of previous therapies, and the patient's expectations. Constraints faced in the treatment of melasma are melasma often recalcitrant to therapy, tendency to recurrence, risk of side effects, long-term treatment and patient compliance, and expensive treatment costs.[3,8,9] Management of melasma is by eliminating risk factors, limiting ultraviolet light, using sunscreen, topical therapy (hydroquinone, arbutin, azelaic acid, vitamin C, kojic acid, retinoids, tretinoin, adapalane, triple combination cream, kligman formula, tranexamic acid), chemical peels, oral tranexamic acid as well as the use of light and laser modalities.[10,11] The current therapy that is being used is Platelet rich plasma (PRP).[1,8,12,13]

Platelet rich plasma is an autologous plasma solution made from the patient's own blood with a high concentration of platelets.[14,15] PRP contains various Growth Factors (GF) which are secreted from activated platelet Granula-α. platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β 1, 2), insulin-like growth factor, adhesion molecules, integrins and several cytokines.[16-18] Transforming growth factor beta is abundant in PRP, It is released in an inactive form from platelet granules and is then activated by proteolytic cleavage. In the skin, TGF-β regulates several cell functions including cell proliferation, differentiation, and melanogenesis.[19] Several studies support the role of TGF-β in regulating melanogenesis. In mouse melanocytes, TGF-β1 significantly suppresses melanin synthesis (melanogenesis) through several mechanisms including delayed activation of Extracellular Signal-Regulated Kinase (ERK).[20,21] Transforming growth factor beta 1 can reduce the activity of tyrosinase, tyrosinase-related proteins and promoters. Microphthalmia Transcription Factor (MITF).[16,22] Several studies have reported that PRP is effective in the treatment of hyperpigmentation.[3,23] Monitoring the effectiveness of this therapy will use the modified Melasma Area Severity Index (mMASI) quantitative rating scale, which is a simple and reliable validation which is a modification of the most commonly used MASI score for melasma.[24]

Material and Methods

Data collection was conducted online through the use of electronic recources such as Medline Pubmed, EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, ClinicalTrials.gov, as well as manual searching from Indonesian libraries over a period of time untill the data analysis were completed. According to the research requirements, the study sample size was all clinical trials with randomization involving the injection of platelet rich plasma in melasma patients.

Inclusion criteria include: Research using platelet rich plasma in melasma patients from 2014 to 2021, in the form of clinical trials with or without control, the subject in the article is mentioned not suffering from dermatitis or skin inflammation at the site of the treatment, the subject in the article is mentioned not pregnant, using oral contraceptives, using Hormone Replacement Therapy (HRT), and having blood clotting disorders or taking anticoagulant drugs,

the study outcome was the mMASI score for meta-analysis, other outcomes related to melasma such as MASI were used in a systematic review. Studies were rejected if they: were not written in Indonesian or English, were case report, serial case, letter, literature review, systematic review.

Research Prosedures

The references and electronic information service cover the databases Medline Pubmed, EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, ClinicalTrials.gov. Other sources include reference lists, conference proceedings, field researchers, and publications. The data scavenging was continued until the data were analyzed.

The following Medical Subject Headings (MeSH) keywords were utilized to generate two citation subcategories.1) platelet rich plasma; (2) melasma. The two subgroups were combined using the Boolean term 'AND' to construct a collection of citations pertinent to the research question The PRISMA flowchart from 2009 was used to conduct the literature search. Three researchers did a separate literature survey, and the citations of all source publications as well as the most current literature review were examined to detect missing articles. Consensus was used to settle any differences in paper selection and data extraction.

Data were extracted separately by three researchers using the supplied data extraction forms. The data recorded were the treatment with Platelet rich plasma and the treatment in the control group and the mMASI score. The quality assessment method was used to evaluate the study's quality for Randomized Clinical Trial Studies-2 (QUADAS-2: A Revised Tool).

Data analysis

Prior to data processing, the collected data will be reviewed for completeness and accuracy. The data will then be entered into the computer. Data on research features such as title and year of research will be presented in the form of data extraction. Treatment data in the form of administration of platelet rich plasma and treatment in the control group as well as the mMASI score will be extracted from the research report and entered into a special research sheet.

The systematic review assessment and meta-analysis of weighted mean differences between the treatment and control groups will be analyzed using the Cochrane systematic review software (Review Manager (RevMan) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Result

The flowchart of the 2009 Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) was used to browse relevant research publications **(Figure 1)**.

Electronic database searches including pubMed, cochrane, scopus, ProQuest, ebscohost, clinical trials and using the search term Medical Subject Headings (MeSH) with platelet rich plasma citations combined with the Boolean “AND” found 60 articles, plus a manual search for articles from other sources obtained 14 articles. The articles obtained were then discussed, there were no articles with the same title and 50 articles were obtained. The articles that have been obtained are then reviewed based on the relevant titles so that 17 appropriate articles are obtained. Of the 17 articles, they were then reviewed and 8 articles were excluded, including

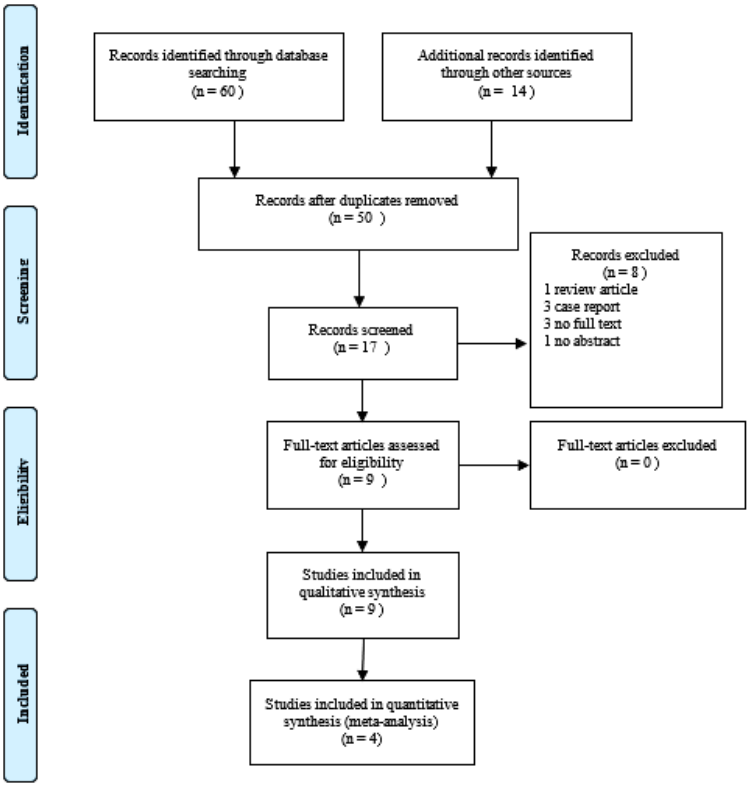

Figure 1 Flowchart of identification and selection of research literature in systematic review and meta-analysis

1 review article, 3 case reports, 3 no full text, and 1 no abstract. So we got 9 articles. A total of 9 full-text articles were reviewed and all articles fulfilled the inclusion requirements, so that 9 articles were involved in the qualitative review (systematic review) and 4 articles were included in the quantitative review (meta-analyses) to determine the effect of PRP administration on scores. mMASI in melasma patients.

Research Characteristics

Descriptive analysis of research characteristics consisted of the country where the study was conducted, the number of samples, the type of therapy or treatment given, the outcome, and the length of the research conducted. The results shown in the table above regarding the characteristics of the study, it was found that the study locations were carried out in Egypt as many as 44.5% (n: 4), India 22.2% (n: 2), Thailand 11.1% (n: 1), Iraq 11.1% (n: 1), and Pakistan 11.1% (n: 1) in the 2015-2020 period. The number of samples included in the study varied from 10-60 research samples. All studies assessed clinical improvement subjectively and/or objectively. Subjectively all melasma patients were assessed with mMASI, hemi-MASI, and MASI scores. While objectively assessed the melanin index, erythema index using Mexameter and the level of wrinkles using Antera.

Therapy in the treatment group was given intradermal injection or topical application before or after microneedling using Dermapen. Therapy is given at a dose of 0.1-1.5 mL in melasma lesions. The study used a comparison group using injection of tranexamic acid 22.2% (n:2), normal saline 11.11% (n:1), tranexamic

acid cream 11.1% (n: 1), topical tranexamic acid before microneedling. 11.1% (n:1), CO_2 laser 11.11% (n:1), with PRP injection after microneedling 11.1% (n:1), and without control 22.2% (n:2). The most length of treatment was 3 months 44.5% (n:4), treatment duration of 2.5 months was 22.2% (n:2), 2 months was 22.2% (n:2), and there was 1 study what is not explained is the length of the study, only the number of research sessions listed is 11.1% (n:1).

Result of Qualitative Data Analysis (Systematic Review)

Nine literatures were analyzed qualitatively.[26-30] Result was presented as follows:

1. Abdelshafy et al in 2017 performed a study on 23 research individuals who were assigned to the experimental group. (n=23) receiving 1 mL PRP injection therapy on the face's left side. the comparison group (n=23) received tranexamic acid injection therapy of 1 mL (4mg/mL) on the face's right side. Therapy was administered intradermally using a 40U/mL 30G insulin needle. The study was conducted in 3 sessions with an interval of 1 month, followed by evaluation for 3 months. Research subjects have an age range of 32-50 years with a mean of 38.35±3.94. Outcomes were analyzed in the form of differences in mean mMASI scores before and after treatment in the two research groups. The study's outcome found a significant decrease in the mean mMASI score from the baseline compared to the end of the treatment. The mean baseline mMASI score in the treatment group was 7.54 ± 4.67 and the end of treatment was 4.6 ± 3.41, while in the control group the mean baseline mMASI score was 6.92±5 and the end of treatment was 28.3±2.97. In this study also explained about side effects in the treatment group, 18 patients (78.3%) had pain at the injection site and 5 patients (21.7%) who felt pain in the injection area and erythema, the same percentage was also found in the group comparison. The authors concluded that PRP injection is a therapeutic modality that can be used for melasma without permanent side effects, but it is less effective than tranexamic acid.
2. Madan et al in 2019 to 2020 arranged a study on 30 melasma patients with the experimental group (n=30) receiving 1mL PRP injection therapy on the face's left side. The comparison group (n=30) received tranexamic acid injection therapy of 1 mL (4mg/mL) on the face's right side. Both PRP and tranexamic acid therapy were administered using a 100U/mL insulin needle injected intradermally in melasma lesions. The study was conducted in 4 sessions with an interval of 21 days and then evaluated for up to 3 months. Research subjects have an age range of 20-50 years. The outcomes analyzed were differences in mean mMASI scores pre and post treatment in the experimental group and comparison group. The outcomes presented a decrease in the mean mMASI score, in the treatment group the mean baseline mMASI score was 7.81±3.17 at the end of therapy, the mean mMASI score was 5.1±1.8, while in the comparison group the mean baseline mMASI score was 7.83±3.18 and at the end of therapy it was 4.5±1.9. The authors concluded that intradermal tranexamic acid showed better improvement than PRP.
3. Sirithanabadeekul et al in 2016 to 2017 performed a study on 10 melasma patients with the experimental group (n=10) receiving 0.1 mL/cm^2 PRP injection therapy. The comparison group (n=10) received normal saline injection therapy. Both are administered intradermally. The study was

conducted in 4 sessions every 2 weeks. The research subjects were 33-58 years old. The study outcomes were mMASI, MASI, hemi-MASI, erythema index and melanin index (measured by Mexameter) and wrinkle level and melanin level as measured by Antera. 3D Analysis. The findings revealed a reduction in the mean of mMASI score, at baseline 4.92±0.96 and at the end of therapy 3.5±0.67 there was an improvement of 28.9% while in the comparison group with a mean baseline mMASI score of 4.98±0.86 and at the end of therapy 4.53±0.96, there was only improvement. 9%. The decrease in mMASI scores was significant between the 2 treatment groups (p=0.42). In the mean melanin index there was a decrease with (p=0.334) with a mean baseline of 256.73±17.68 and at the end of therapy 238.63±16.4 in the treatment group, while in the comparison group it increased, the mean baseline was 246.57±22.88 and at the end of therapy 249.47±21.36, although this change was considered insignificant (P=0.849). In the mean melanin level, there was a significant decrease (p=0.38) with a baseline mean of 0.61±0.02 and at the end of therapy 0.57±0.03 in the treatment group. There was a significant decrease in the level of wrinkles in the treatment group, with a baseline mean of 10.47±1.26 and 7.63±1.06 at the end of therapy (P=0.40). Neither the level of melanin nor the level of wrinkles changed significantly in the control group. The erythema index did not increase significantly with the mean baseline 320.6±13.75 and end of therapy 322.02±13.27 (P=0.938). Meanwhile, the comparison group also improved not significantly from 322.3±18.94 at baseline and 327.0±13.99 (P=0.802). The investigators concluded that PRP injection was significantly beneficial in reducing melasma lesions compared to the control group.

4. Gamea et al in 2020 arranged a study on 40 melasma patients with the control group (n=20) receiving 1 mL PRP intradermal injection therapy and 5% tranexamic acid cream in a liposome-based cream and the control group (n=20) receiving tranexamic acid cream therapy 5% in liposome-based cream only. PRP injection was given using a 32 G needle. The study was conducted in 4 sessions every 3 weeks. Subjects in the study had an age of 34-55 years in the treatment group and 34-58 years in the comparison group. mMASI study outcomes and patient satisfaction. The outcomes presented the mean baseline mMASI in the treatment group was 12.1± 2.9 (P=<0.001) and at the end of treatment 3.6±1.9 and in the control group 11.7±2.98 and at the end of therapy 4.8±1.9 showed significant improvement (P=<0.01). Patient satisfaction in this study in the treatment group was 50% quite satisfied (n=10), 25% very satisfied (n=5), 15% less satisfied (n=3), 10% dissatisfied (n=2). Meanwhile, the control group was not satisfied 55% (n=11), 20% less satisfied (n=4), very satisfied 15% (n=3), and quite satisfied 10% (n=2). The side effects reported in the treatment group with tranexamic acid cream and PRP injection were mostly 60% of patients experienced moderate pain during PRP injection, 50% had transient erythema for several hours after injection, and 1 patient (5%) experienced hyperpigmentation after treatment. While in the group that only used tranexamic acid cream it was reported to be very safe, only 10% (n=2) experienced re-pigmentation within one month after therapy. it is associated with recurrent/ persistent melasma. Researchers concluded that topical 5% tranexamic acid cream is considered as a melasma treatment

technique which is both safe and effective. Platelet rich plasma is a potential and safe therapeutic modality to improve the therapeutic efficacy of tranexamic acid in the treatment of melasma, because the combination gives better results than topical tranexamic acid alone.

5. Jassim et al in 2019 conducted a study involving 30 melasma patients with an age range of 20-43 years. The study was conducted by giving 1 mL of PRP injection therapy intradermally to melasma lesions on the face. PRP injection is given using a 30G needle. This study only consisted of one group, the treatment group, not having a control group, which was conducted for 3 months with 2-week intervals. The study results measured the difference in mean mMASI baseline and end of therapy. Mean mMASI baseline was 15.41±3.66 and at the end of therapy 8.67±3.07 with (P=0.0006). The investigators concluded that intradermal administration of PRP injection in melasma patients showed significant improvement which could be assessed by decreasing mean mMASI.
6. Hofny et al in 2018 reported a study in 23 melasma patients with a treatment group (n=23) treated with 1 mL topical PRP application after microneedling on the face's right side and a control group (n=23) treated with 1 mL intradermal PRP injection using 100U/mL insulin needle with 4 mm mesoneedle on the face's left side. This procedure was carried out in 3 sessions with a 4 week break between each session. The mean age of the research subjects was 32.35±5.87. The study outcomes assessed were the mean scores of mMASI, MASI, hemi-MASI. The study's outcomes present a decrease in the mMASI score in the treatment group by 5.71±2.56 at baseline and at the end of therapy 2.90±2.05 (P=0.000). The mean MASI score at baseline was 11.86± 5.25 and at the end of therapy 6.96±4.82 (P=0.000), while the mean right-sided hemi-MASI at baseline was 6.31±2.73 and at the end of therapy 3.57±2.49 (P=0.000) and the mean hemi-MASI side was left face baseline 5.73±2.77 and at the end of therapy 3.40±2.49 (P=0.000). They also reported the level of patient satisfaction, 39.1% very satisfied, 39.1% satisfied, slightly satisfied 13.1% and 8.7% dissatisfied. The researcher concluded that the mMASI score has decreased, the MASI score pre and post treatment and a decrease in the mean hemi-MASI score on both face's sides, where the experimental group and the control group gave significant improvements. However, the difference in values between the two sides of the face is not significant. Very good improvement was obtained, respectively, 39.1% and 30.4% on the left and right sides of the face. The side effects reported by the majority of the study subjects felt considerable discomfort on the left side of face treated with PRP therapy with mesoneedling compared to dermapen. Downtime (erythema, swelling, and pain) was less on the face's left side than on the right side of the face. Injection However, researchers evaluated these two methods by assessing the hemi-MASI score to compare the two methods of PRP application, it was found that the right side of the face treated with microneedling was slightly better than the the face's left side that was given PRP with dermapen.
7. Faiz et al in 2015 reported a study on 15 melasma patients with a treatment group without a control group. The research subjects were given 1 mL PRP intradermal injection therapy using a 30G needle. The treatment was given for 3 months with an interval of 2 weeks. The research subjects were 21-42 years old. Study results were assessed by the difference in the mean

MASI scores pre and post treatment. The mean baseline MASI score was 15.71±6.81 and at the end of therapy 4.98±2.13 (P=0.0000). This study also reported no serious or persistent side effects and only mild (almost imperceptible) erythema in 2 study subjects. Researchers mentioned that PRP injection therapy for melasma has a good therapeutic effect, but has not achieved effective results due to limited sessions. Researchers recommend melasma therapy using PRP as adjuvant therapy but for monotherapy the results are not too significant.

8. Gharib et al in 2019 conducted a study on 26 melasma patients aged 29-50 years, divided into two groups, the treatment group (n=13) given PRP topical therapy after microneedling with dermapen. While the control group (n=13) was given topical application of tranexamic acid after microneedling with dermapen. The treatment in this study was 4 sessions but the duration was not stated. The outcomes analyzed were differences in the mean MASI scores before and after treatment in the two treatment groups. The mean baseline MASI score for the treatment group was 6.84±3.37 and at the end of therapy 3.08±1.99 (P=0.002). The control group had a mean baseline of 9.06±2.95 and end of treatment 5.89±3.41 (P = 0.004). The study results showed a 50% improvement from the start and end of therapy. The difference in MASI scores between the 2 groups was (P= <0.017). In this study it was stated that PRP therapy with microneedling showed better results than therapy with tranexamic acid.
9. Bohara et al in 2017-2018 conducted a study with 60 melasma patients who were then separated into two groups, the treatment group (n=30) given 1.5 mL PRP intradermal injection therapy on the face. The control group (n=20) was given 10,600 nm fractional CO_2 laser therapy (Energy: 70-120mJ, duration 3 minutes, and intervals of 10ms. The study was conducted in 4 sessions for 2.5 months with 15 days interval. The age of the research subjects was above 18 years of age. The analyzed outcomes were MASI scores and Visual Analog Scale (VAS). The difference from the baseline MASI score of the CO_2 laser showed a zigzag line where the PRP line dropped to zero level which means that CO_2 laser treatment creates more variability in MASI scores were probably caused by the pattern of therapy and drugs. In contrast, the MASI scores of PRP showed very little variability which indicates the outcome of therapy was not or less effective. VAS scores were assessed by two raters, each for the treatment group obtained 90% not there was a change and 76.7% no change, while the control group obtained 40% good and 36.7 moderate. Based on this percentage, the MASI score and the VAS score in find the group treated with CO_2 was more effective than the group treated with PRP injection. The level of patient satisfaction was also directly proportional to the MASI and VAS scores, which showed that the group given CO_2 therapy was better than the PRP injection group. The investigators concluded that CO_2 therapy was more effective than PRP injection. However, in patients treated with CO_2 more pigmentation was found again. The reported side effects of CO_2 therapy are erythema and burning on laser, and pain when injected with PRP.

Qauntitative Data result (Meta- Analysis)

The difference in the average mMASI scores of pre and post treatment in the experimental group getting Platelet Rich Plasma and the comparison group is presented in **Table 1**.

Table 1 The difference in mean mMASI scores before and after treatment in the treatment group that received Platelet Rich Plasma injection

No	*Name of the research*	*Control type*	*Treatment*		*control*	
			Average±SD	*n*	*Average±SD*	*n*
1	Madan, 2021	TA injection	-2,71±2,95	30	-3,33±2,98	30
2	Abdelshafy, 2019	TA injection	-2,94±4,55	23	-4,09±4,68	23
3	Sirithanabadeekul, 2019	NS injection	-1,42±0,93	10	-0,45±1,00	10
5	Gamea, 2020	Topical TA	-8,5±2,76	40	-3,37±2,82	40

TA: tranexamic acid, NS: Normal saline

Table 2. The results of the meta-analyses of the effectiveness of PRP therapy compared with controls on the mMASI score in melasma patients.

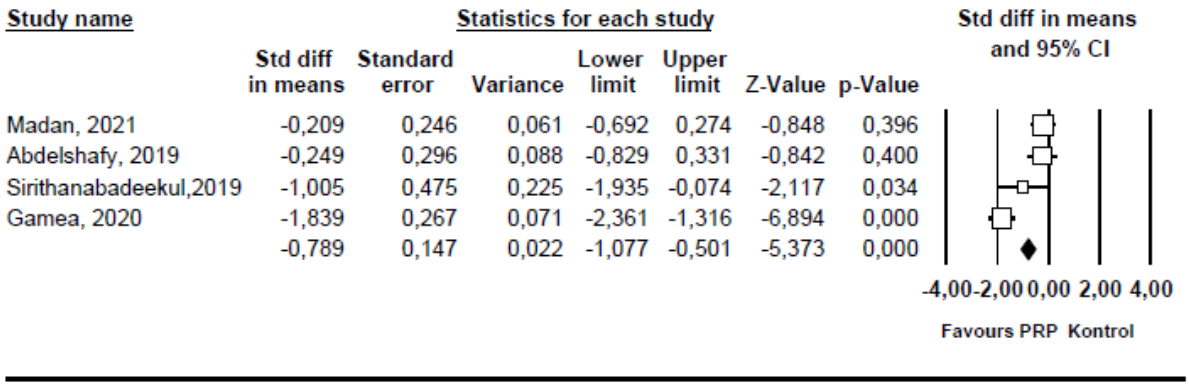

Table 1 shown, the mean distinction of mMASI scores pre and post treatment in the studies involved in the PRP injection therapy group was negative. This indicates a decrease in the mMASI score after treatment with PRP injection. In the control group, the mean difference in mMASI scores following the delivery of control treatment, all results were negative. This demonstrates that when treatment was administered to the control group, the mMASI score decreased as well. The greatest decrease in mMASI scores in the Gamea study, 2020 with PRP injection treatment and topical tranexamic acid was -8.5±2.76, and the smallest was in the Sirithanabadeekul study, 2019 in the control group who received normal saline injection, which was -1.42±0.93.

The meta-analysis outcomes of the potential of PRP injection therapy compared to controls for melasma therapy can be seen in **Table 2**.

Table 2 shows the meta-analysis outcomes of the potential of PRP therapy compared with controls on the mMASI score of melasma patients. The results of the heterogeneity test showed the value of Q value=24,564, df=3; p<0.001, I2=87.787. This shows that the data are heterogeneous, but by the results of statistical Q test and heterogeneity, the I2 test yielded p<0.001, suggesting that the data is homogenous. Since the data were homogenous, the analysis was performed using a fixed effect model. The meta-analysis revealed that the statistical Q value was z value=-5.373 (p=<0.001). This demonstrates that PRP injection in general can dramatically lower the mMASI score.

Table 2 shows the difference in the total mean mMASI -0.789±0.147 (95% CI=-1.077 to –0.501) in the meta-analysis. Meaning that the mMASI score after PRP treatment was lower than the control, yet the difference was statistically significant (p=0.001).

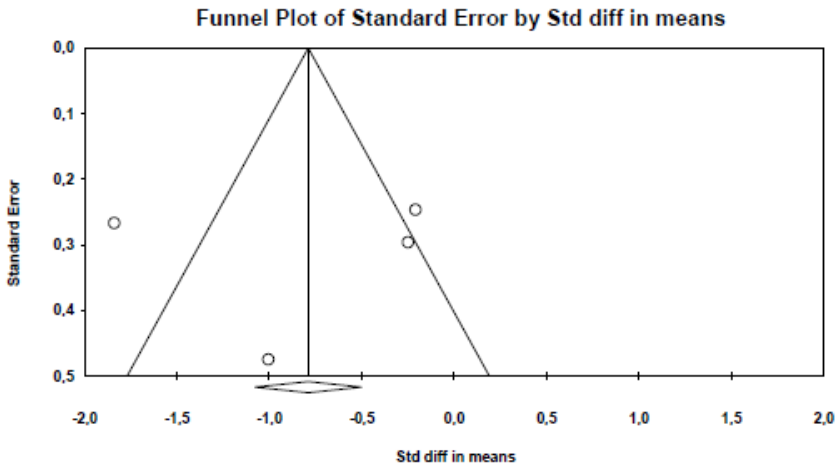

Figure 2 Funnel plot using 4 studies on the effectiveness of PRP therapy with Tranexamic Acid in melasma patients.

Tabel 3 Risk of bias in studies used for systematic reviews and metaanalyses.

	Random sequence generation	*Allocation concealment*	*Selective reporting*	*Other bias*	*Blinding (participants and personnel)*	*Blinding (outcome assessment)*	*Incomplete outcome data*	*Overall*
Abdelshafy, et al	?	?	+	?	?	?	+	-
Madan, et al	?	?	+	?	?	?	+	-
Sirithanabadeekul, et al	?	?	+	+	+	+	+	?
Gamea, et al	?	?	+	?	?	?	+	-
Hofny, et al	?	?	+	+	?	+	+	-
Gharib, et al	?	?	+	?	?	?	+	-
Bohara, et al	+	+	+	+	-	+	+	?

Circle symbol of ● with a positive sign indicating a low risk of bias, circle symbol of ● with a question mark the risk of bias cannot be assessed, circle symbol of ● with a negative sign indicates a high risk of bias.

The overall results were unaffected by a sensitivity analysis that excluded one of the involved studies in the meta-analysis. PRP continued to provide a substantial decrease in the mMASI score (p=0.001), according to the overall data. **Figure 2** depicts an evaluation of the occurrence of publication bias.

Figure 2 visually, the funnel plot is symmetrical to the normalized distinction in mean score on the zero line rightward. Two studies are shown on the left. This statistically indicates that there is no a file-drawer effect.

Bias Risk from the involved studies

Based on data on study characteristics, the research articles included in the meta-analysis were 4 studies, study by Abdelshafy et al 2017, Madan et al 2021, Sirithanabadeekul et al 2019, Gamea et al 2020. which reported differences in mean mMASI before and after treatment with PRP. The research of Jassim et al 2020, Faiz et al 2015 cannot be meta-analyzed because it does not have a control group, there is only a treatment group, while Gharib et al 2019, and Bohara et al 2019 cannot be meta-analyzed because they have different outcomes, MASI. Hofny et al could not be meta-analyzed because in the control group the therapy was given the same but different methods of administration.

The risk assessment of bias in the studies included in this study is shown in **Table 3**.

Sirithanabadeekul et al and Bohara et al does not obviously define that "blinding" is performed in the research setting, thus it cannot be assessed as high or low risk. The other studies were assessed as a whole with high risk because many were not mentioned in the study so they could not be assessed. Studies that do not have controls also cannot be assessed for risk of bias. Based on the table above, it can be concluded that there are no studies that have good quality evidence. 2 studies with evidence quality that cannot be assessed (28.6%). While 5 studies with low quality of evidence (71.4%).

Discussion

The aim of this study is to investigate the effect of administering platelet rich plasma on the modified melasma area severity index (mMASI) score in melasma patients using an observational meta-analytic study, a systematic review, and a meta-analysis. 9 studies were involved in the qualitative systematic review and 4 of them could be reviewed (meta-analyzed) to determine the effect of autologous conditioned plasma treatment on Modified Melasma Area Severity Index (MMASI) scores in melasma patients.

Both studies conducted by Jassim et al 2020, Faiz et al 2015 cannot be meta-analyzed because they do not have a control group, there is only a treatment group, while Gharib et al 2019, and Bohara et al 2019 cannot be meta-analyzed because they have different outcomes, MASI. Hofny et al could not be meta-analyzed because in the control group the therapy was given the same but different methods of administration

The studies that were included in both systematic reviews and meta-analyses had different age ranges of study subjects in each study. Age range in the study Abdelshafy et al 32-50 years, Madan et al 20-50 years, Sirithanabadeekul et al 33-58 years, Gamea et al 34-55 years, Jassim et al 20-43 years, Hofny et al Mean age 32.35±5.87, Faiz et al age 21-42 years, Gharib et al age 29-50 years, Bohara et al Age of research subjects is above 18 years. Five studies involved both sexes in research subjects, the remaining 4 studies only used women as research subjects. In studies that used both sexes, it showed that it was more in women than men. Fitzpatrick's skin type also varied between II-V research subjects.

Based on the literature, melasma can occur in all races, can affect both men and women. The ratio of melasma sufferers in men and women in Indonesia is 24:1.[5] Melasma accounts for 50% of aesthetic cases in Asia.[4,25] Melasma can occur between the ages of 30-55 years, and is often found in women of active reproductive age. Melasma often occurs in Fitzpatrick types of complexions of III to V dwell in high-UV-light-intensity settings. This skin type is found in Hispanic, Asian, and African descent.[11]

Therapy in the treatment group was given intradermal injection of PRP either by injection

in the lesion area or by topical application after the use of dermapen. in one of the studies conducted by Hofny et al compared the two methods of administration by assessing the hemi-MASI score, it was found that therapy with microneedling was slightly better than that given PRP with dermapen. Administration of PRP at a dose of 1-1.5 mL.

The results of the analysis in all studies conducted revealed an alleviation in the average scores of mMASI and MASI. The results of the study conducted by Abdelshafy et al showed a considerable reduction in the mean mMASI score from the baseline compared to the end of the treatment. The average baseline mMASI score in the treatment group was 7.54±4.67 and the end of treatment was 4.6±3.41, while in the control group the mean baseline mMASI score was 6.92±5 and the end of treatment was 28.3±2.97.

The results of the study by Madan et al showed a reduction in the mMASI average scores, in the treatment group the mean baseline mMASI score was 7.81±3.17 at the end of therapy, the mean mMASI score was 5.1±1.8, while in the comparison group the mean baseline mMASI score was 7.83± 3.18 and at the end therapy was obtained 4.5±1.9.

Sirithanabadeekul et al reported a decrease in the mean mMASI score, at baseline 4.92±0.96 and at the end of therapy 3.5±0.67 there was an improvement of 28.9% while in the comparison group with a mean baseline mMASI score of 4.98±0.86 and at the end of therapy 4.53±0.96, there was improvement only 9%. The decrease in mMASI scores was significant between the 2 treatment groups (p=0.42). Gamea et al showed mean baseline mMASI in the treatment group 12.1±2.9 (P=<0.001) and at the end of treatment 3.6±1.9 and in the control group 11.7±2.98 and at the end of therapy 4.8±1.9 showed significant improvement (P=<0.01). Significant findings were also delivered by Jassim et al and Hofny et al where there was a decrease in mean mMASI after treatment. This shows that the mMASI score is lower after treatment than before and is in accordance with the hypothesis.

The literature states that PRP contains various Growth Factors (GF) which are secreted from activated platelet Granula-α. transforming growth factor beta (TGF-β 1, 2), insulin-like growth factor, platelet-derived growth factor (PDGF), adhesion molecules, integrins and several cytokines.[16-18] TGF- controls a variety of cell processes, covering differentiation, proliferation, and melanogenesis.[19] Several studies support the role of TGF-β in controling melanogenesis. In mouse melanocytes, TGF-β1 remarkably suppresses melanin synthesis (melanogenesis) through a range of methods including delayed activation of Extracellular Signal-Regulated Kinase (ERK).[20,21]

Transforming growth factor beta 1 can lower the activity of tyrosinase, the promoter of Microphthalmia Transcription Factor (MITF), and tyrosinase-related proteins. TGF-β can delay ERK activation and suppress the expression of Paired-Box Homeotic Gene (PAX) that regulates melanogenesis due to UV rays.[16,22] Monitoring the effectiveness of this therapy will use the modified Melasma Area Severity Index (mMASI) quantitative rating scale, which is a simple and reliable validation that is a modification of the most commonly used MASI score for melasma.[24]

The treatment group in all studies was given PRP therapy while in the control group varied, compared to the administration of tranexamic acid injection, tranexamic acid cream, normal saline injection, and CO_2 laser. One study in the experimental group and the comparation group gave the same PRP injection but differed in the

way it was administered. In a study conducted by Sirithanabadeekul et al delivered the mean mMASI value in the comparation group before and after treatment there was a decrease but not statistically significant. Meanwhile, the study conducted by Abdelshafy et al, Madan et al, Gamea et al, Hofny et al showed a significant change in the mean mMASI in the control group. While the study of Gharib et al, and Bohara et al also presented substantial changes in the control group, only the parameter used was MASI. The studies by Jassim et al and Faiz et al did not have a control group.

Three studies, by Abdelshafy et al, Madan et al and Bohara et al concluded that the decrease in mMASI and MASI scores before and after the PRP group was not higher than the control group. This means that tranexamic acid injection and CO_2 laser are more effective than PRP injection. Another study by Sirithanabadeekul et al stated that the PRP injection group was better than the control group. This shows that PRP injection is better than normal saline because it is a placebo. The study by Jassim could not be assessed because it did not have a control. While the rest use the MASI score as a parameter. Gharib et al. stated that melasma patients, topical PRP administration after microneedling with Dermapen was better than tranexamic acid topical administration after microneedling, this was seen from the comparison of the mean MASI in the two groups.

Conclusion

Based on the meta-analysis and systematic review outcomes, it can be implied that in the group who got PRP intradermal injection therapy, there was a significant decrease in the mMASI score after treatment. The decrease in mMASI scores in the group given platelet rich plasma was lower than the control group given tranexamic acid injection in melasma patients.

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