



American Journal of Dermatological Research and Reviews (ISSN:2638-1893)



The Effectiveness of Pulsed Dye Laser in Management of Acne Vulgaris: A Systematic review and meta-analysis

Maya Rahmanita^{*1}, Retno Indar Widayati¹, Puguh Riyanto¹, Asih Budiastuti¹, Diah Adriani Malik¹, Muslimin¹, Hardian²

¹Departement of Dermatovenereology, Faculty of Medicine, Diponegoro University / Dr. Kariadi Hospital, Dr. Sutomo street No. 16 Semarang-Indonesia. ²Department of Physiology, Faculty of Medicine, Diponegoro University.

ABSTRACT

Background: Acne vulgaris is one of the most prevalent skin diseases, affecting up to 85% of teenagers and young adults. Multiple treatment options including topical, systemic or physical therapies. However, the effects of conventional therapies are limited due to antibi-otic resistance and adverse effects such as irritation and teratogenicity of isotretinoin. Light-based therapy is an alternative and/or adjuvant therapy in patients who cannot tolerate or unresponsive to conventional therapies that may provide fewer side effects, patient com-fort, fast onset of action, and with equal or greater effectiveness. We aimed to assess the effectiveness of using Pulsed Dye Laser as a treatment option for acne vulgaris. A systemat-ic Review and Meta-analysis was performed of randomized clinical trials assessing the ef-fectiveness of Pulsed Dye Laser in management of acne vulgaris. **Methods:** Medline Pubmed, Scopus, Cochrane library, the reference list, conference pro-ceedings, researchers in field of eligible studies were searched. Eight studies (n=275 sub-jects) were included in qualitative analysis of which six studies (n=190 subjects) were in-cluded in meta-analysis. The mean age of the participant was 21,94 years old. Intervention using application of Pulsed dye laser as monotherapy or combination in acne vulgaris pa-tients with follow-up at least 12 weeks. and the outcomes is a decrease mean of acne vul-garis lesions counts after received pulsed dye laser therapy. **Results:** Pooling of data using random effects model showed that the group that received PDL therapy alone or in combination had a lower number of acne lesions than the control group with the mean difference was -0.593 (95% CI = -1.290 to 0.104), the z value was -1.668 with p = 0.095. This shows that the number of lesions in the group that received sin-gle or combined PDL therapy was lower than the control group. However the difference is insignificant. **Conclusion.** From the results of the systematic review conducted, it can be concluded that in the group given Pulsed Dye Laser therapy there was a decrease in the total number of acne vulgaris lesions compared to before treatment, and the decrease, which was indicated by the difference in the mean number of acne lesions, was significantly greater compared to the control who was only given placebo. Pulsed Dye Laser therapy can be an alternative treatment option for acne vulgaris in patients who are unresponsive to previous treatment or conditions where there are contraindications to systemic therapy.

Keywords: pulsed dye laser, acne vulgaris

*Correspondence to Author:

Maya Rahmanita

Departement of Dermatovenereology, Faculty of Medicine, Diponegoro University / Dr. Kariadi Hospital, Dr. Sutomo street No. 16 Semarang-Indonesia.

How to cite this article:

Maya Rahmanita, Retno Indar Widayati, Puguh Riyanto, Asih Budiastuti, Diah Adriani Malik, Muslimin,Hardian. The Effectiveness of Pulsed Dye Laser in Management of Acne Vulgaris: A Systematic review and meta-analysis. American Journal of Dermatological Research and Reviews, 2021, 4:41

 **eSciPub**
eSciPub LLC, Houston, TX USA.
Website: <https://escipub.com/>

Introductions

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicle characterized by polymorphic lesions. The prevalence of acne is estimated at about 85% in adolescents and young adults (12-25 years). Acne vulgaris is the third most common case that comes for treatment at the Central General Hospital and Regional General Hospital in Indonesia and is 15.3% of the 10 most skin diseases in 2008-2013 at the Dr. Kariadi Semarang.¹⁻⁴

Acne vulgaris therapy can be in the form of topical therapy, systemic therapy or physical therapy. Acne therapy, both topical and systemic, can have side effects in the form of skin irritation, bacterial resistance, and potential teratogenic effects. Light-based therapy is an alternative and/or adjuvant therapy in patients who cannot tolerate or are unresponsive to conventional therapy that may provide fewer side effects, patient comfort, rapid onset of action, and with equal or greater effectiveness.⁵⁻⁷

Pulsed Dye Laser has been reported to be effective in the treatment of inflammatory acne. *P. acnes* colonization is associated with the development of inflammatory acne lesions. Pulsed Dye Laser in acne vulgaris is thought to activate the bacterial porphyrin, causing oxidative damage to *P. acnes* reducing bacterial colonization and acne lesions. Pulsed Dye Laser can be used either as a single therapy or in combination with other therapies both topical, systemic and physical.⁷⁻⁹

Pulsed Dye Laser in acne vulgaris is thought to be secondary to damage to *P. acnes* via activating bacterial porphyrin. The use of Pulsed dye laser for acne therapy is still controversial. Seaton et al. (2003) suggested an improvement in acne lesions compared to placebo. Leheta (2009) compared PDL therapy with topical therapy (tretinoin, benzoyl peroxide) or chemical peels (trichloroacetic acid 25%) where there were significant improvements in all three groups with a higher remission time in the PDL

group. Orringer et al (2004) gave PDL therapy to half of the face area there was no significant change compared to the untreated face area.⁸⁻¹¹

Currently, there have been many studies on the effectiveness of Pulsed Dye Laser therapy on acne vulgaris, but there has been no systematic review and meta-analysis assessing the effectiveness of using Pulsed Dye Laser as a therapy for acne vulgaris. Based on this background, researchers are interested in conducting a systematic review and meta-analysis to assess the effectiveness of Pulsed Dye Laser in the management of acne vulgaris.

Methods

Literature Search

The following databases were searched until the time of data analysis: Medline Pubmed, Scopus, Cochrane library. The reference list, conference proceedings, researchers in field of eligible studies were searched to identify additional studies.

The following Mesh terms were used for searching: "Pulsed Dye Laser" AND "*acne vulgaris*". Literature search was performed by three reviewers independently using PRISMA flow diagram 2009.¹² Differences in opinion were resolved between all reviewers to reach consensus.

Inclusion criteria were: clinical trials with/without randomization on individuals or split faces, adolescence to adulthood, both men and women with all degrees of acne, intervention : used pulsed dye laser therapy modalities either as monotherapy or in combination in acne vulgaris patients, follow up for at least 12 weeks, outcomes: mean difference number of acne vulgaris lesions before and after treatment.

Studies were excluded if they: were written neither in Indonesian nor English, were case report, serial case, letter, literature review.

Study Selection

Three reviewers conducted the study selection independently. Duplicate articles were removed. Title and abstract review, full-text review were

assessed for eligibility using the predefined inclusion and exclusion criteria. Differences in opinion were resolved between all reviewers to reach consensus.

Data extraction

Data extraction were performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only.¹³ Differences in opinion during data extraction were resolved between all reviewers and consensus was reached.

Assessment of risk of bias

Risk-of bias assessment were performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only¹³ and The Cochrane Collaboration's tool for assessing risk of bias in randomized trials.¹⁴

Data synthesis

Meta-analysis difference in weighted mean was conducted using Comprehensive Meta-Analysis A Computer Program for meta-analysis Version 3.3. Where data was not available to enable pooling, a descriptive synthesis was performed.

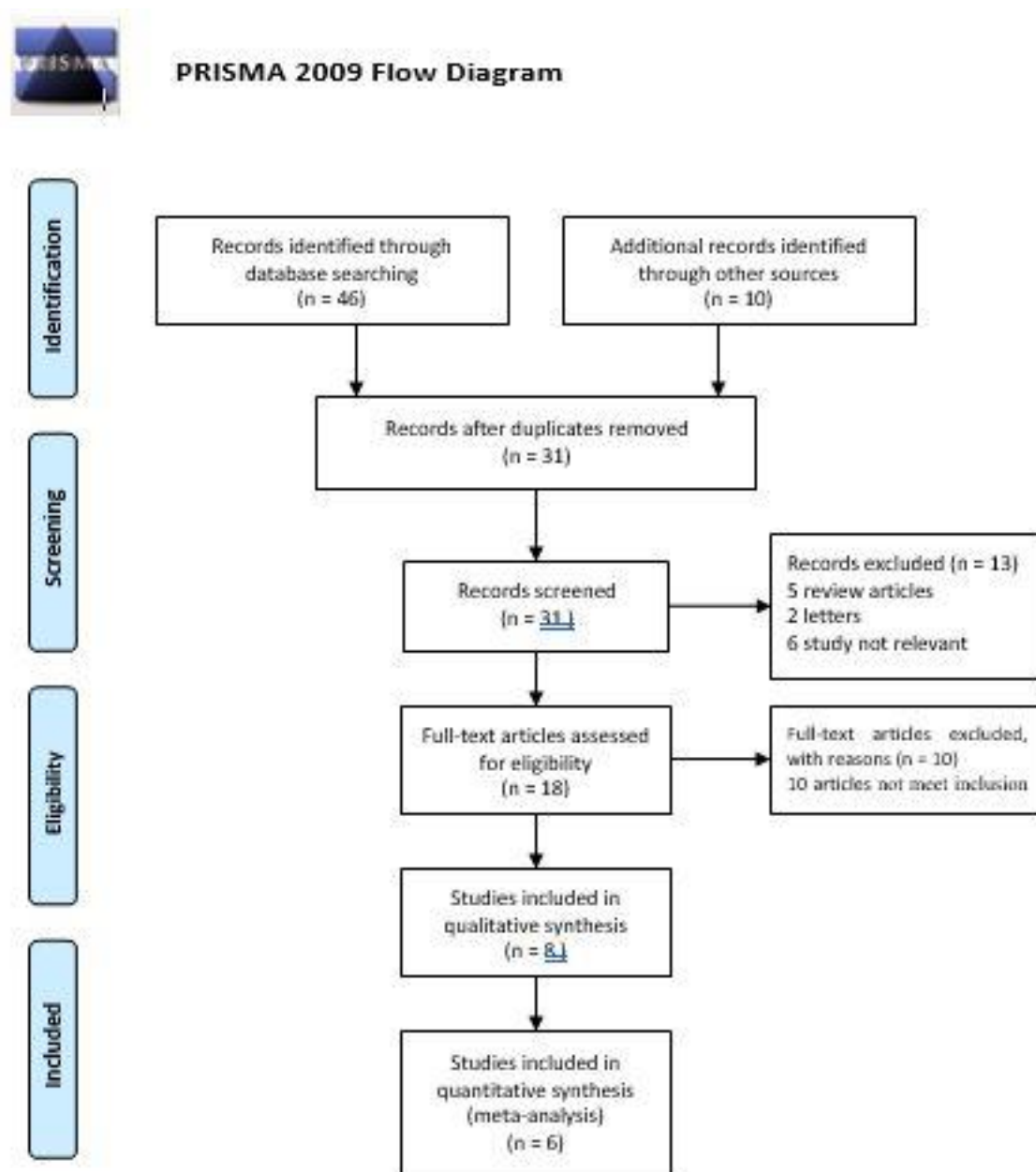


Figure 1. PRISMA flow diagram

Table 1. Characteritics of included studies

Study	Mean age	N recruited/ analyzed	Intervention Group	Comparison Group	Duration of Intervention	Outcome
Jeffrey et al 2004	13-31 years (mean 20,7 years)	40/26	the following parameters: wavelength 585 nm, pulse duration 350 μ sec, spot size 7 mm, fluence of 3 J / cm^2	Half of other untreated side of the face.	One or 2 nonpurpuric pulsed dye laser treatments	Mean number of acne vulgaris lesions. (papules, pustules, cysts, comedones, and erythematous macules) Leeds mean total score.
Nataya Voravutinon et al 2016	16-43 years (mean 22,32 years)	62/55	Subpuric (low fluence) PDL therapy for half of the face with parameters: wavelength 595 nm, pulse duration 6 msec, spot size 10 mm, fluence 4 J / cm^2 (subpuric/ low fluence)	PDL midpuric therapy (high fluence) to the other half of the face with the following parameters: wavelength 595 nm, pulse duration 6 msec, spot size 10 mm, fluence 6-7.5 J/ cm^2 (midpurpuric /high fluence)	4 treatments with intervals 3 weeks.	Mean total number of acne vulgaris lesions. Satisfaction scale with therapy (no change, minimum, moderate, good, maximum)
Manal Mohamed Salah el din et al 2016	>16 years	30/30	PDL therapy to half of the face PDL with parameters: wavelength 585 nm, pulse duration 40 ms, spot size 10 mm, fluence 7.5-8 J/ cm^2	Half of the left side of the face was given 585/1064 nm combination laser therapy. YAG Nd Parameters: wavelength 1,064 nm, pulse duration 40 ms, spot size 10 mm, fluence 40 J / cm^2	4 treatments with intervals 2 weeks.	Mean number of inflammatory and non- inflammatory lesions of acne vulgaris. Mean severity of acne (Cook et al, 2009 grading)
Mona Soliman 2020	18-29 years (mean 23 years)	15/15	PDL therapy on the right side of the face Parameters: wavelength 585 nm, pulse duration 350 μ sec, spot size 7 mm, fluence of 3 J / cm^2	left side of the face was given topical methylene blue nanoemulgel for 10 min, followed by a laser diode parameter: Wavelength 665-nm, power 150 mW, spot size 5 mm, intensity 765 mW / cm^2	3 treatments with intervals 2 weeks.	Mean number of inflammatory and non- inflammatory lesions of acne vulgaris. Mean severity of acne (Leeds revised acne grading system)
Jeffrey S Orringer, et all 2010	15-50 years (mean 25 years)	44/29	topical photosensitizer (20% 5-aminolevulinic acid) and PDL on the left or right side of the face, with parameters: wavelength 595 nm, pulse duration 10 ms, spot size 10 mm, fluence 6.5 - 7.5 J / cm^2	Half of other untreated side of the face.	3 treatments with intervals 2 weeks.	Mean number of acne vulgaris lesions. (papules, pustules, cysts, open comedones, closed comedones and erythematous macules) Mean severity of acne (modified Leeds acne severity scale)
Wafaa H. Borhan et all 2014	18-25 years (mean 21,3 years (group 1) and 21,05 years (group 2))	40/40	administration of PDL + traditional topical antibiotics with parameters: wavelength 595 nm, pulse duration 350 msec, spot size 5/7 mm, fluence 4 J / cm^2	Administration of traditional topical antibiotic therapy only	3 treatments with intervals 4 weeks	Mean number of acne vulgaris lesions.
I. García-Morales 2009	14-43 years (mean 22,16 years)	50/50	long pulse PDL on the half of the face, with parameters: wavelength 595 nm, pulse duration 6 ms, fluence 2 J / cm^2	long pulse PDT (Methylaminolevulinat e + long-pulse PDL) on the half of the face,	4-6 treatments with intervals 4 weeks	Mean total number of acne vulgaris lesions Mean number of inflammatory and non- inflammatory lesions. Percentage of satisfaction with therapy results Percentage of side effects from therapy
A Harto, et all 2007	14 – 35 years (mean 20 years)	36/30	PDL therapy with parameters: wavelength 585 nm, pulse duration 350 μ sec, fluence of 2,5 J / cm^2	compared with the number of baseline lesions before treatment	3 treatments with intervals 4 weeks	Mean number of inflammatory and non- inflammatory lesions of acne vulgaris

Results

Initial database searches identified 31 non duplicate records. 13 were excluded during title/abstract review, 10 were excluded during

Study Characteristics

The characteristics of included studies are given in Table 1.

The study was conducted in Michigan, USA (n = 2), Thailand (n = 1), Cairo (n = 3), Madrid (n = 2) in the period 2004-2020. Research in the form of a split face (n = 6), and on individuals (n = 2). The total sample of 8 studies was 275 people, with an age range of 14-50 years, with a mean age of 21.94 years from 7 studies, while one study did not mention the mean age of the subjects. All studies included subjects with clinical mild (n = 1), mild-moderate (n = 2), moderate-severe (n = 2), mild-severe (n = 3) acne vulgaris. Treatment of PDL therapy either as a single therapy (n = 6), or in combination with other therapies (n = 2), follow up for at least 12 weeks. Pulsed Dye Laser parameters used include low fluence, 2-4 J / cm² (n = 6), and high fluence, 6.5–8 J / cm² (n = 2). The frequency of treatment was 1-2 sessions (n = 1), 3 sessions (n = 4), 4 or more sessions (n = 3).

1. Jeffrey S Oringer 2004⁸ conducted a study on 40 research subjects with the Group1 treatment group (n = 20) getting 1x PDL therapy session on half of the face and the group2 treatment group (n = 20) getting 2x PDL therapy sessions on the half side of the face randomly randomized to determine which side of the face to be given therapy and the number of sessions given, and the comparison group was half the other side of the face that was not given therapy. Subjects were followed up every two weeks, for 12 weeks. Outcomes were analyzed before and after treatment (in mean) with a 95% confidence interval which was the mean number of acne lesions, including lesions (papules, pustules, cysts, blackheads, and macular erythematosis), and the degree of acne severity was measured by the Leeds acne severity scale. on the treated and untreated side of the face. There was a decrease in the number of papules on the

full-text review. Eight studies were included in this review, of which 6 studies were included for meta-analysis. Figure 1 gives details of the study selection process.

treated face area (baseline and week 12; 10,7 and 6,6) and a decrease in the number of papules on the untreated face area (baseline and week 12; 8,7 and 6,5). Increased number of pustules in treated facial areas (baseline and week 12; 2,1 and 2,7) and decreased number of pustules in untreated facial areas (baseline and week 12; 2,1 and 1,9). Increased number of comedones in treated facial areas (baseline and weeks 12; 33 and 35) and increased numbers of comedones in untreated facial areas (baseline and weeks 12; 34 and 36). Decreased number of cysts in treated facial areas (baseline and week 12; 1,5 and 1,4) and Increased number of cysts in untreated facial areas (baseline and week 12; 1,2 and 1,5). Increased number of erythematous macules in treated facial areas (baseline and week 12; 30 and 35) and increased number of erythematous macules in untreated facial areas (baseline and week 12; 26 and 30). In the graph, it was found that there was no significant difference in the change in the number of lesions from baseline to week 12 in the treated and untreated facial areas. Decreased Leeds scores for treated facial areas (baseline and week 12; 4 and 13.9 and no change in Leeds scores for untreated facial areas (baseline and week 12; 3,8 and 3,8). series with the Leeds grading score (range, 1-12), did not show a significant difference in the mean face area treated (baseline and week 12; 4 and 3,9) compared with untreated face area (baseline and week 12). ; 3,83 and 3,79), (P> 0.99). The authors concluded that non-purpuric pulsed dye laser therapy did not show any significant improvement in acne, more research is needed to recommend pulsed dye laser therapy as a treatment for acne.

2. Nataya Voravutinon, et al, 2016 conducted a study on 62 research subjects with treatment of low fluence PDL therapy on half of the face and compared with the provision of high fluence PDL

therapy on the other half of the face for 4 times of therapy sessions with intervals of 3 weeks. Subjects were followed up every 3 weeks, for 12 weeks. Outcomes were analyzed before and after treatment (in mean) in the form of the mean number of acne lesions, the patient satisfaction scale for therapy with a questionnaire on the side of the face treated with low fluence and high fluence PDL. There was a significant reduction in the number of lesions with low fluence PDL therapy (baseline and week 21; 18,82 and 11,58) a significant reduction in the number of lesions with high fluence PDL therapy (baseline and week 21; 18,47 and 11, 23). In the graph, it was found that there was no significant difference in changes in the number of lesions from baseline to week 21 in facial areas receiving low fluence and high fluence PDL therapy. Patient satisfaction scale to therapy results in an increase in satisfaction scores after low fluence PDL therapy (visit 4 and 7 visits; 1 subject and 2 subjects (felt there was no change in lesions), 1 subject and 5 subjects (minimal change), 14; subjects and 17 subjects (moderate change), 31 subjects and 20 subjects (good), and 8 subjects and 11 subjects (maximum change) Increased satisfaction scores after high fluence PDL therapy (visits 4 and 7 visits; 1 subject and 0 subjects (felt that there was no change in the lesion), 1 subject and 4 subjects (minimal change), 11 subjects and 18 subjects (moderate change), 35 subjects and 22 subjects (good), and 8 subjects and 10 subjects (maximum change) The scale of patient satisfaction with therapy, there was no significant difference between the types of therapy received and the mean score of patient satisfaction with therapy, there was an increase in the score of satisfaction with therapy after the second therapy both in low fluence and high fluence PDL therapy. a side effect of post-inflammatory hyperpigmentation in 5 subjects with Fitzpatrick V skin type. The authors concluded that PDL was effective in reducing low and high fluence acne lesions. However, there was no significant difference between the

number of acne lesions in low fluence and high fluence PDL therapy.

3. Manal Mohamed Salah el din, et al 2016. conducted a study on 30 research subjects with single PDL therapy on the right side of the face and compared with the 585/1064-nm laser combination therapy on the left side of the face for 4 times of therapy sessions with 2 week intervals. Subjects were followed up every 2 weeks, for 12 weeks, and 6 months. Outcomes were analyzed before and after treatment (in mean \pm standard deviation (SD)) in the form of the mean number of inflammatory acne lesions, the mean number of non-inflammatory acne lesions, and the mean change in the degree of acne severity as measured by Cook et al, 2009 grading⁴⁰ at half side of the face treated with PDL and half of the face treated with the 585/1064-nm combination laser. The results were a significant reduction in the number of inflammatory acne lesions on the right-sided face with PDL therapy (baseline, week 12, and 6 months; 11.4 ± 6.3 , 1.3 ± 1.2 , and 0.9 ± 1.1), a significant reduction in the number of inflammatory acne lesions with 585/1064-nm laser combination therapy (baseline, week 12, and 6 months; 11.3 ± 6.2 , 1.3 ± 1.1 , and 0.8 ± 0.8). There was no statistically significant difference in the reduction in the number of inflammatory acne lesions between the two treatment modalities. Significant reduction in the number of non-inflammatory acne lesions on the right-sided face with PDL therapy (baseline, week 12, and 6 months; 5.1 ± 4.2 , 1.7 ± 2.5 , and 1.7 ± 2.4), a significant reduction in the number of non-inflammatory acne lesions with 585/1064-nm combination laser therapy (baseline, week 12, and 6 months; 4.5 ± 3.8 , 1 ± 2 , and 1 ± 1.9). There was no statistically significant difference in the reduction in the number of non-inflammatory acne lesions between the two treatment modalities. Significant reduction in the severity of acne on right-sided face with PDL therapy (baseline, week 12, and 6 months; 5.2 ± 1.6 , 1.2 ± 1.3 , and 0.6 ± 1.2), a significant decrease in the severity of acne on right-sided

face with 585/1064-nm laser combination therapy (baseline, week 12, and 6 months; 5.2 ± 1.6 , 1.1 ± 1.3 , and 0.6 ± 1.2). There was no statistically significant difference in the reduction in the severity of acne between the two treatment modalities. The authors concluded that PDL therapy and the combination PDL / Nd: YAG can be used as an effective, safe, and well-tolerated treatment option for inflammatory and non-inflammatory acne therapy.

4. Mona Soliman, et al, 2020 conducted a study on 15 research subjects with PDL therapy on the right side of the face and compared with PDT therapy (topical methylene blue nanoemulgel + 665-nm diode laser) on the left side of the face for 3x therapy sessions at intervals of 2 weeks. Subjects were followed up every 2 weeks, up to 6 weeks and 12 weeks. Outcomes were analyzed before and after treatment (in mean \pm standard deviation (SD)) in the form of the mean number of inflammatory acne lesions, the mean number of non-inflammatory acne lesions, and the mean severity of acne using the Leeds acne severity scale on the right side of the face treated with PDL and compared with PDT therapy (topical MB nanoemulgel + 665-nm diode laser) on $\frac{1}{2}$ the left side of the face. There was a significant reduction in the number of inflammatory acne lesions with PDL therapy (baseline, week 6, and week 12; 15.20 ± 8.33 , 3.73 ± 1.16 , and 3.33 ± 1.34), a significant reduction in the number of inflammatory acne lesions with PDT (topical therapy). MB nanoemulgel + 665-nm diode laser) at (baseline, week 6, and week 12; 17.2 ± 9.96 , 5.47 ± 4.76 , and 3.60 ± 3.13). Significant reduction in the number of non-inflammatory acne lesions with PDL therapy (baseline, week 6 and week 12; 11.47 ± 9.49 , 2.33 ± 2.35 , and 1.2 ± 1.61), a significant reduction in the number of lesions with PDT therapy (topical MB nanoemulgel + 665-nm diode laser) at (baseline, week 6, and week 12; 12 ± 10.03 , 6.67 ± 6.99 , and 3.80 ± 4.26). There was no statistically significant reduction in the number of inflammatory and non-inflammatory acne lesions compared to

baseline for the two treatment modalities. There was no significant difference in decreasing the number of acne lesions in PDL and PDT therapy. A significant reduction in the severity of acne with PDL therapy (baseline, week 6, and week 12; 6.13 ± 2.44 , 3.27 ± 1.91 , and 3.00 ± 1.93), a significant reduction in the number of lesions with PDT therapy (topical MB nanoemulgel + 665-nm laser diode) at (baseline, week 6, and week 12; 6.13 ± 2.44 , 1.87 ± 1.68 , and 1.60 ± 1.64). There was a statistically significant decrease in the severity of acne treated with PDT compared with PDL. Treatment-related side effects with PDL on the right side of the face included mild-moderate pain, erythema, crusting in almost all subjects, and post-inflammatory hyperpigmentation in nearly half of the subjects. In contrast, therapy with PDT on the left side of the face did not reveal erythema, pain, peeling, swelling, crusting, post-inflammatory hyperpigmentation or scarring during or after therapy. The authors concluded that PDL and MB-PDT are effective in acne therapy, MB in nanoemulgel form is a promising treatment approach for acne. Treatment with MB-PDT gave better results than PDL, in less pain during therapy, and minimal side effects. PDL is effective in mild inflammatory lesions, preferably with a simultaneous benefit against acne scars and a reduced incidence of acne scar formation, but with more side effects such as pain and hyperpigmentation.

5. Jeffrey S Oringer, et al, 2010 conducted a study on 44 research subjects with the K1 treatment group (n = 24) getting 3x sessions of 20% 5-aminolevulinic acid + PDL on $\frac{1}{2}$ of the left side of the face and the K2 treatment group (n = 20) received 3x therapy sessions of 20% 5-aminolevulinic acid + PDL on $\frac{1}{2}$ of the right side of the face, with intervals of 2 weeks, and a comparison group of $\frac{1}{2}$ of the other side of the face that was not given therapy. Subjects were followed up every two weeks, for 16 weeks. Outcomes were analyzed before and after treatment (in mean) with a 95% confidence interval which was the mean number of acne

lesions, including lesions (papules, pustules, cysts, closed comedones, open comedones, and macular erythematosis), and the degree of acne severity was measured by Leeds acne severity scale on treated and untreated side of the face. There was a decrease in the number of papules in the treated facial area (baseline and week 16; 13.31 and 11.52) and a decrease in the number of papules on untreated facial areas (baseline and week 16; 13.66 and 12.69). Decreased number of pustules in treated facial areas (baseline and week 16; 6.45 and 3.90) and decreased number of pustules in untreated facial areas (baseline and week 16; 6.38 and 3.76). Decreased number of cysts in treated facial areas (baseline and week 16; 0.45 and 0.83) and increased number of cysts in untreated facial areas (baseline and week 16; 0.62 and 0.86). Decreased number of closed comedones in treated facial areas (baseline and week 16; 29,24 and 22,28) and decreased number of closed comedones in untreated facial areas (baseline and week 16; 29,38 and 25,31). Decreased number of open comedones in treated facial areas (baseline and week 16; 15.00 and 10.21) and decreased number of open comedones in untreated facial areas (baseline and week 16; 16.07 and 9.28). Decreased number of erythematous macules in treated facial areas (baseline and week 16; 22,29 and 16,39) and decreased number of erythematous macules in untreated facial areas (baseline and week 16; 21,71 and 19,21). In the graph, it was found that there was no significant difference in the change in the number of lesions from baseline to week 16 in the treated and untreated facial areas. The number of erythematous macules decreased bilaterally from baseline to week 16, the mean reduction in the number of erythematous macules was more statistically significant in treated facial areas compared to untreated ones. Decreased severity of acne in treated facial areas (baseline and week 16; 3,63 and 2,56), decreased severity of acne in untreated facial areas (baseline and week 16; 3,59 and 3.07). The severity of acne decreased from baseline to week 16 bilaterally

in both treated and untreated facial areas. There was a statistically significant difference in the severity of acne on the treated face compared to the untreated area. The authors concluded that PDT therapy may be of benefit to patients with inflammatory acne. PDT with PDL can be used as a second or third line treatment option in patients with inflammatory acne who have not responded to traditional therapy. Decreased number of erythematous macules in treated facial areas (baseline and week 16; 22,29 and 16,39) and decreased number of erythematous macules in untreated facial areas (baseline and week 16; 21,71 and 19,21). In the graph, it was found that there was no significant difference in the change in the number of lesions from baseline to week 16 in the treated and untreated facial areas. The number of erythematous macules decreased bilaterally from baseline to week 16, the mean reduction in the number of erythematous macules was more statistically significant in treated facial areas compared to untreated ones. Decreased severity of acne in treated facial areas (baseline and week 16; 3,63 and 2,56), decreased severity of acne in untreated facial areas (baseline and week 16; 3,59 and 3.07). The severity of acne decreased from baseline to week 16 bilaterally in both treated and untreated facial areas. There was a statistically significant difference in the severity of acne on the treated face compared to the untreated area. The authors concluded that PDT therapy may be of benefit to patients with inflammatory acne. PDT with PDL can be used as a second or third line treatment option in patients with inflammatory acne who have not responded to traditional therapy.

6. Wafaa H. Borhan, et al. 2014 conducted a study on 40 research subjects with the treatment group (n = 20) by administering topical antibiotic therapy and PDL for 3 therapy sessions at 4 week intervals, compared to the control group (n = 20) who treated with topical antibiotics alone. Subjects were followed up every 4 weeks, for 12 weeks. Outcomes were analyzed before and after treatment (in mean \pm standard deviation

(SD)) as the mean number of acne lesions in subjects treated with the combination of PDL and topical antibiotics, then compared with the number of acne lesions in subjects treated with topical antibiotics alone. The results were a decrease in the number of acne lesions in subjects with combination therapy of PDL and topical antibiotics (baseline, and week 12; 25.7 ± 5.88 and 8.75 ± 2.91), a decrease in the number of acne lesions after topical antibiotic therapy alone (baseline, and week 12; 25.75 ± 6.71 and 17.7 ± 5.14). There was a statistically significant difference in the reduction in the number of acne lesions from baseline before and after therapy in the combined group of topical antibiotics and PDL and topical antibiotics only group. There was a significant difference in the number of acne lesions between the two groups after therapy. There were 19 subjects (95% subjects) showing significant improvement, while 1 subject (5%) showed moderate improvement in the group receiving topical antibiotic therapy and PDL. There were 19 subjects (95% subjects) showing minimal improvement and 1 subject (5%) showing moderate improvement. The authors concluded that PDL therapy was effective in controlling acne vulgaris lesions by decreasing the number of acne lesions.

7. I. García-Morales, et al, 2009 conducted a study on 50 research subjects with PDL treatment on $\frac{1}{2}$ of the face and compared with PDT therapy (topical Methylaminolevulinate + PDL) on the other half of the face for 4-6x therapy sessions with 4 week intervals. Subjects were followed up every 4 weeks. Outcomes were analyzed before and after treatment (in mean \pm standard deviation (SD)) in the form of the mean total number of acne lesions, the mean number of inflammatory acne lesions, the mean number of non-inflammatory acne lesions, and the pain scale measured on a scale of 1-6 on $\frac{1}{2}$ side. PDL-treated face and compared with PDT (topical methylaminolevulinate + PDL) therapy on the other half of the face. There was a significant reduction in the total number of acne lesions with PDL therapy (baseline, week 12;

$20.06 \pm 11,771$, and $15.10 \pm 11,329$), a significant reduction in the total number of acne lesions with PDT therapy (topical methylaminolevulinate + PDL) at (baseline, and week 12; 23.12 ± 13.133 and 13.38 ± 11.283). A significant reduction in the number of inflammatory acne lesions with PDL therapy (baseline, week 12; $10.32 \pm 7,266$ and $7.96 \pm 7,148$), a significant reduction in the total number of inflammatory acne lesions with PDT (topical methylaminolevulinate + PDL) therapy at (baseline, and week 2). 12; $13.30 \pm 8,286$, and $7.00 \pm 6,893$). A significant reduction in the number of non-inflammatory acne lesions with PDL therapy (baseline, week 12; $9.54 \pm 5,797$, and $6.90 \pm 5,515$), a significant reduction in the total number of non-inflammatory acne lesions with PDT (topical methylaminolevulinate + PDL) therapy at (baseline, and week 12; 9.60 ± 6.376 , and $6.36 \pm 5,267$). Statistically, there was a significant reduction in the total number of acne lesions on half of the face receiving PDL therapy by 21.94%. A significant reduction in the total number of acne lesions on $\frac{1}{2}$ of the face received PDT therapy by 44.39%. There was a greater reduction in the total number of acne lesions in the facial area treated with PDT compared to PDL alone. Statistically, there was a significant reduction in the number of inflammatory acne lesions on half of the face receiving PDL therapy by 17.05%. A significant reduction in the total number of inflammatory acne lesions on $\frac{1}{2}$ of the face received PDT therapy by 48.97%. There was a greater reduction in the total number of inflammatory acne lesions in the facial area treated with PDT compared with PDL alone, but did not show a statistically significant difference. 7. I. García-Morales, et al, 2009 conducted a study on 50 research subjects with PDL treatment on $\frac{1}{2}$ of the face and compared with PDT therapy (topical Methylaminolevulinate + PDL) on the other half of the face for 4-6x therapy sessions with 4 week intervals. Subjects were followed up every 4 weeks. Outcomes were analyzed before and after treatment (in mean \pm standard deviation (SD)) in the form of the mean total number of

acne lesions, the mean number of inflammatory acne lesions, the mean number of non-inflammatory acne lesions, and the pain scale measured on a scale of 1-6 on ½ side. PDL-treated face and compared with PDT (topical methylaminolevulinate + PDL) therapy on the other half of the face. There was a significant reduction in the total number of acne lesions with PDL therapy (baseline, week 12; $20.06 \pm 11,771$, and $15.10 \pm 11,329$), a significant reduction in the total number of acne lesions with PDT therapy (topical methylaminolevulinate + PDL) at (baseline, and week 12; 23.12 ± 13.133 and 13.38 ± 11.283). A significant reduction in the number of inflammatory acne lesions with PDL therapy (baseline, week 12; $10.32 \pm 7,266$ and $7.96 \pm 7,148$), a significant reduction in the total number of inflammatory acne lesions with PDT (topical methylaminolevulinate + PDL) therapy at (baseline, and week 2). 12; $13.30 \pm 8,286$, and $7.00 \pm 6,893$). A significant reduction in the number of non-inflammatory acne lesions with PDL therapy (baseline, week 12; $9.54 \pm 5,797$, and $6.90 \pm 5,515$), a significant reduction in the total number of non-inflammatory acne lesions with PDT (topical methylaminolevulinate + PDL) therapy at (baseline, and week 12; 9.60 ± 6.376 , and $6.36 \pm 5,267$). Statistically, there was a significant reduction in the total number of acne lesions on half of the face receiving PDL therapy by 21.94%. A significant reduction in the total number of acne lesions on ½ of the face received PDT therapy by 44.39%. There was a greater reduction in the total number of acne lesions in the facial area treated with PDT compared to PDL alone. Statistically, there was a significant reduction in the number of inflammatory acne lesions on half of the face receiving PDL therapy by 17.05%. A significant reduction in the total number of inflammatory acne lesions on ½ of the face received PDT therapy by 48.97%. There was a greater reduction in the total number of inflammatory acne lesions in the facial area treated with PDT compared with PDL alone, but did not show a statistically significant difference.

8. A Harto, et al 2007 conducted a study on 36 research subjects treated with PDL therapy in 3 sessions with 4 week intervals. Subjects were followed up every 4 weeks, for 12 weeks. Outcomes were analyzed before and after treatment in the form of mean number of inflammatory acne lesions, mean number of non-inflammatory acne lesions, in subjects treated with PDL, then compared with the number of inflammatory and non-inflammatory acne lesions at baseline. The results were a decrease in the number of inflammatory acne lesions after PDL therapy (baseline, and week 12; 49,17 and 20,97), a decrease in the number of non-inflammatory acne lesions after PDL therapy (baseline, and week 12; 42,50 and 30, 23). There was a statistically significant reduction in the number of acne lesions compared to baseline before therapy was administered. The authors concluded that PDL therapy was effective in providing clinical improvement in the form of a reduction in the number of inflammatory and non-inflammatory acne lesions with the greatest improvement in decreasing inflammatory lesions.

Risk of Bias in included studies

Based on the data on the characteristics of the study, the research articles that will be included in the meta-analysis are 6 studies, namely Jeffrey S Orringer et al 2004, Manal Mohamed Salah el din et al 2016, Mona Soliman et al 2020, Jeffrey S Orringer et al 2010, Wafaa H. Borhan et al 2014, and I García-Morales et al. 2009 reported the mean number of acne lesions pre and post treatment. A Harto et al. 2007 study did not report the number of lesions as an outcome. Based on this, research by A Harto et al. 2007 could not be included in the meta-analysis.

The risk assessment of bias from 6 studies included in the meta-analysis using The Cochrane Collecting data - form for RCTs only 41 and The Cochrane Collaboration's tool for assessing risk of bias in randomized trials 42 included means of randomization, allocation concealment, blinding of study subjects, blinding outcomes. Incomplete outcome data, the

selection of reported outcomes, and other biases are shown in Table 2 .

Meta-analysis

Meta-analysis of the subgroup analysis of the combination therapy group PDL (Orringer JS, 201 and Borhan WH, 2014) found that there was a difference in the mean number of acne vulgaris lesions after therapy between the treatment group and the control group, the difference was not significant with a mean difference of -0.885 (95% CI = -2.039 to 0.269), the Z value is 1.503 and $p = 0.133$. The mean difference value was negative, this indicates that the number of acne lesions after PDL combination therapy was lower than the control group, but the difference was not significant. Meta-analysis of the PDL therapy subgroup alone (the study of Salah MM, 2016, Soliman M, 2020, Morales IG, 2009 and Orringer JS, 2004) found differences in the mean number of acne vulgaris lesions after therapy between the treatment group and the control group, the difference is also insignificant with the mean difference was -0.426 (95% CI = -1.300 to 0.449), the Z value was -0.954 and $p = 0.340$. The mean difference value was negative, this indicates that the number of acne lesions after treatment with PDL alone was lower than that of the control group, but the difference was not significant.

The results of the overall analysis showed that the group that received PDL therapy alone or in combination had a lower number of acne lesions than the control group with the mean difference was -0.593 (95% CI = -1.290 to 0.104), the z value was -1.668 with $p = 0.095$. This shows that the number of lesions in the group that received single or combined PDL therapy was lower than the control group. However the difference is insignificant. (Figure 2)

Discussion

This study is an observational meta-analytic study, systematic review and meta-analysis to determine the effectiveness of Pulsed Dye Laser therapy in the management of acne vulgaris.

The prevalence of acne is estimated at around 85% in adolescents and young adults (12-25 years), with the greatest peak age in adolescents aged 16-19 years in men or 14-17 years in women. However, acne can continue into adulthood. The prevalence of acne in adult individuals is about 5%. Whereas in adult individuals, 64% of acne was reported in their 20s and 43% in their 30s. Acne is a clinically dynamic condition and is influenced by both intrinsic factors (genetic, racial, hormonal) and extrinsic factors (stress, climate/ temperature/ humidity, cosmetics, diet, and drugs), which can result in spontaneous improvement or flare.^{1-4,15}

Laser is one of the adjuvant therapies that are given especially to patients who refuse or cannot tolerate or are not responsive to standard therapy. In general, this therapy has several primary targets, including: (1) reducing the number of P.acnes, (2) disrupting the function of the sebaceous glands, (3) anti-inflammatory. Pulsed Dye Laser emits light in the visible light spectrum (yellow light) , which selectively absorbs oxyhemoglobin, produces selective photothermolysis of blood vessels associated with inflammatory processes in acne. Absorption of light causes photoexcitation of porphyrin and produces highly reactive, cytotoxic free radical specimens, which in turn cause P. acnes damage.¹⁶⁻²⁰

The use of topical photosensitizers has the potential to enhance the effects of light-based therapy. Several studies have reported the success of PDT on acne. Liga Hongcharu and colleagues demonstrated a significant improvement in back acne in patients treated with aminolevulinic acid and red light. Horfelt et al. showed a 54% reduction in inflammatory acne lesions compared with 20% of controls in PDT-treated skin with methyl aminolevulinic and red light. Oral and topical therapies have been shown to be effective in the treatment of acne. Topical therapies used include retinoids, antibiotics, antimicrobials, azelic acid and salicylic acid. Systemic therapy includes doxycycline, azithromycin, and quinolones.^{2,21}

The Voravotinon N, et al. Study evaluating PDL therapy by comparing the level of subpuric fluence (low) with the level of purpuric fluence (high) showed a significant reduction in the

number of acne lesions compared to baseline, but found no significant difference in the number of acne lesions between the two groups.²²

Table 2. Risk of bias of included studies in meta-analysis

	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Selective reporting	Incomplete outcome data	Other bias	Overall
Jeffrey S Orringer, dkk 2004	+	+	+	+	+	?	+	+
Manal Mohamed Salah el din, dkk 2016	-	-	?	?	+	?	?	-
Mona Soliman, dkk, 2020	-	-	-	-	+	+	?	-
Jeffrey S Orringer, dkk, 2010	?	?	+	+	+	-	-	-
Wafaa H. Borhan, dkk 2014	?	-	-	-	+	+	?	-
I. García-Morales, dkk 2009	-	-	-	-	+	+	?	-

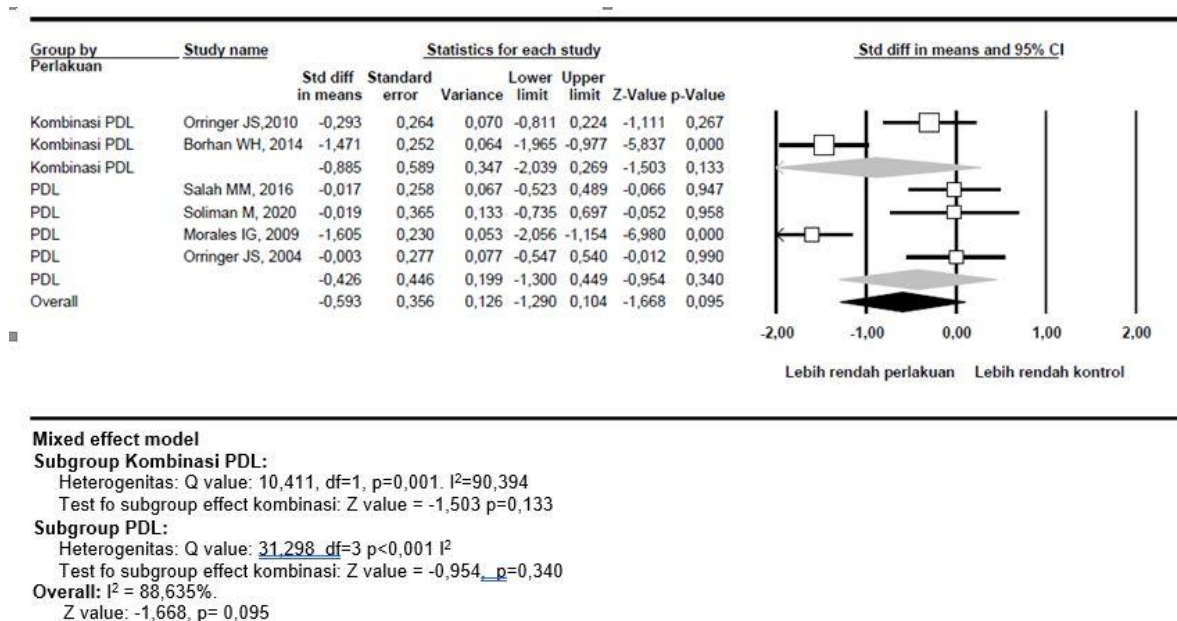


Figure 2. The results of the meta-analysis of the effectiveness of Pulsed Dye Laser therapy on the number of acne vulgaris lesions

The results of the analysis in the research of Jeffrey et al. 2010 showed a significant decrease in the number of erythematous macules in the treated face area compared to controls who did not receive therapy. In general, there was a mild reduction of each lesion subtype (papules, pustules, open comedones, and closed comedones) at week 16 when compared to baseline. Harto, et al. 2007 found a significant reduction in the number of inflammatory and non-inflammatory acne lesions compared to baseline, with the greatest improvement in decreasing inflammatory lesions. Oxyhemoglobin in vasodilated blood vessels in acne lesions serves as a chromophore for Pulsed Dye Laser.^{21,23}

The results of the analysis in the study by Manal Mohamed Salah el din, 2016 showed a significant decrease in the number of inflammatory and non-inflammatory lesions both with PDL therapy and laser combination 585/1064, but there was no significant difference in the reduction in the number of inflammatory and non-inflammatory lesions between the two treatment modalities. I. García-Morales, et al., 2009 found a significant reduction in the total number of acne lesions, both inflammatory and non-inflammatory on PDL and PDT (MAL-PDL) therapy, with a greater reduction in the total number of acne lesions on PDT (MAL) therapy. -PDL), compared to PDL only. There was no statistically significant difference between the two groups. Mona Soliman, et al, 2020 found that there was no significant decrease in the number of inflammatory and non-inflammatory acne lesions compared to the baseline for PDL and PDT therapy (MB-665-nm diode laser), as well as a significant difference in decreasing the number of acne lesions in the two treatment modalities. Wafaa H. Borhan, et al. 2014 found a significant difference in the reduction in the number of acne lesions from the baseline before and after therapy in the combination group of topical antibiotics and PDL, and the group with topical antibiotics only. There was a significant

difference in the number of acne lesions after therapy between the two groups.^{11,24-26}

The use of topical photosensitizers has the potential to enhance the effects of light-based therapy. Endogenous photodynamic therapy (PDT) using different light sources has been shown in clinical trials to be effective for the treatment of mild to moderate inflammatory acne by acting against porphyrins produced by bacteria (*Propionibacterium acne*) alone. Efforts to enhance photodynamic reactions and potentially treat moderate to severe inflammatory acne have begun to use exogenous PDT by applying a topical photosensitizing agent to the area to be treated prior to irradiation. The effect of PDT on *P. acnes* occurs when the light source activates porphyrin produced by bacteria, producing singlet oxygen and free radicals, which cause cellular damage by destroying lipids from the cell membrane.^{2,21,24}

Conclusion

Results of the systematic review conducted, it can be concluded that in the group given Pulsed Dye Laser therapy there was a decrease in the total number of acne vulgaris lesions compared to before treatment, and the decrease, which was indicated by the difference in the mean number of acne lesions, was significantly greater compared to the control who was only given placebo. So that the Pulsed Dye Laser therapy can be an alternative treatment option for acne vulgaris in patients who are unresponsive to previous treatment or conditions where there are contraindications to systemic therapy.

Acknowledgement

The author thanks to all reviewers (Dermatovenereology residents Diponegoro University/ Dr. Kariadi Hospital, Semarang-Indonesia) for their help in collecting and analyzing data.

Funding

Nil.

Conflict of Interest

There is no conflict of interest

Abbreviations :

PDL: Pulsed Dye Laser

RCT : Randomized Controlled Trial

Mesh: Medical subject headings

PRISMA: Preferred Reporting Items for Systematic Review and Meta Analysis

PDT : Photodynamic Therapy

Nd: YAG : neodymium-doped atrium aluminum garnet.

References

1. Susanto S. Epidemiologi Akne Vulgaris. In: Seminar dan Workshop Penanganan Akne Vulgaris. Semarang.
2. KSDKI. Pedoman Tata Laksana Akne di Indonesia. edisi 2nd. Wasitaatmadja SM, Arimuko A, Norawati L, Bernadette I, Legiawati L, editors. Jakarta: KSDKI; 2016.
3. Carolyn Goh, Carol Cheng, George Agak, Andrea L Zaenglein, Emmy M Graber, Diane M Thiboutot JK. Acne Vulgaris. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. Fitzpatrick's Dermatology. 9th ed. new york: McGraw Hill; 2019. p. 1391–412.
4. Bernadette I. Patogenesis Akne Vulgaris. In: Wasitaatmadja SM, editor. Akne. Jakarta: FK UI; 2018. p. 1–6.
5. Group W, Zaenglein AL, Pathy AL. Guidelines of care for the management of acne vulgaris. J Am Dermatology. 2007;56:651–63.
6. Thiboutot D, Gollnick H, Alliance G, Diane M, Finlay A, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. J Am Acad Dermatol. 2009;60(5).
7. Fox L, Csongradi C, Aucamp M, Du Plessis J, Gerber M. Treatment modalities for acne. Molecules. 2016;21(8):1–20.
8. Orringer JS, Kang S, Hamilton T, Schumacher W, Cho S, Hammerberg C, et al. Treatment of Acne Vulgaris With a Pulsed Dye Laser. Am Med Assoc. 2004;291(23).
9. Seaton ED, Charakida A, Mouser PE, Grace I, Clement RM, Chu AC. Pulsed-dye laser treatment for inflammatory acne vulgaris: randomised controlled trial. Lancet. 2003;362:1347–52.
10. Leheta TM. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. J Cosmet Laser Ther. 2009;11(2):118–24.
11. Mohamed M, Samy NA, Salem AE. Comparison of pulsed dye laser versus combined pulsed dye laser and Nd: YAG laser in the treatment of inflammatory Acne Vulgaris. J Cosmet Laser Ther. 2016;4172(December).
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7).
13. Higgins J TJ. Collecting data - form for RCTs only. In: Higgins J TJ, editor. Cochrane Handbook for Systematic Reviews of Interventions Version 510 [Internet] [Internet]. The Cochrane Collaboration; 2011. Available from: <https://training.cochrane.org/data-collection-form-rcts>
14. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(7829):1–9.
15. Suva MA, Patel AM, Sharma N. A Brief Review on Acne Vulgaris: Pathogenesis, Diagnosis and Treatment. STM Journals. 2016;4 (3)(January 2015).
16. Rajabi-Estarabadi A, Eber AE, Nouri K. Laser and light therapies for acne. Lasers dermatology Med dermatologic Appl. 2018;227–36.
17. Liu A, Moy RL, Victor Ross E, Hamzavi I, Ozog DM. Pulsed dye laser and pulsed dye laser-mediated photodynamic therapy in the treatment of dermatologic disorders. Dermatologic Surg. 2012;38(3):351–66.
18. Forbat E, Al-Niaimi F. Nonvascular uses of pulsed dye laser in clinical dermatology. J Cosmet Dermatol. 2019;18(5):1186–201.
19. Karsai S, Roos S, Hammes S, Raulin C. Pulsed dye laser: What's new in non-vascular lesions? J Eur Acad Dermatology Venereol. 2007;21(7):877–90.
20. Pei S, Inamadar AC, Adya KA, Tsoukas MM. Light - based therapies in acne treatment. Indian Dermatol Online J. 2015;6(3):145–58.
21. Orringer JS, Sachs DL, Bailey E, Kang S, Hamilton T, Voorhees JJ. Photodynamic therapy for acne vulgaris: A randomized, controlled, split-face clinical trial of topical aminolevulinic acid and pulsed dye laser therapy. J Cosmet Dermatol. 2010;9(1):28–34.
22. Voravutinon N, Rojanamatin J, Sathwani D, Iyengar S, Alam M. A comparative split-face study using different mild purpuric and subpurpuric fluence level of 595-nm pulsed-dye laser for treatment of moderate to severe acne vulgaris. Dermatologic Surg. 2016;42(3):403–9.
23. Harto A, García-Morales I, Beldar P, Jaén P. Pulsed Dye Laser Treatment of Acne. Study of Clinical Efficacy and Mechanism of Action. Actas Dermo-Sifiliográficas (English Ed [Internet]. 2007;98(6):415–9.

24. García-Morales I, Harto A, Fernández-Guarino M, Jaén P. Photodynamic therapy for acne: Use of the pulsed dye laser and methylaminolevulinate. *Actas Dermosifiliogr* [Internet]. 2010;101(9):758–70.
25. Soliman M, Salah M, Fadel M, Nasr M, El-Azab H. Contrasting the efficacy of pulsed dye laser and photodynamic methylene blue nanoemulgel therapy in treating acne vulgaris. *Arch Dermatol Res* [Internet]. 2020;(0123456789).
26. Wafaa H. Borhan HAH and NHA. Efficacy of Pulsed Dye Laser on Acne Vulgaris. *Implement Sci*. 2014;10(3):67–73.

