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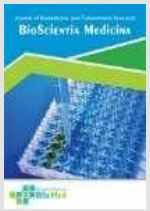

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Adapalene-Benzyl Peroxide Combination as an Option for Acne Vulgaris Treatment: A Systematic Literature Review

Rizkia Chairani Asri[1*], Desy Nofita[2]

[1]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Department of Physiology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

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***Corresponding author:**
Rizkia Chairani Asri

E-mail address:
rizkiachairaniasri@med.unand.ac.id

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A B S T R A C T

Background: Acne vulgaris affect 9,4% of the world population, especially in teenage age. Treatment of acne is based on severity; mild acne is treated with a topical agent, whereas moderate and severe acne is treated with topical and systemic agents. Topical therapy, including retinoids, antibiotics, and benzoyl peroxide, is the foundation of acne treatment. Adapalene-benzoyl peroxide therapy can be used in treatment to avoid antibiotic resistance. This study aimed to evaluate the efficacy and tolerance of adapalene/benzoyl peroxide topical treatment in mild to moderate acne vulgaris **Methods**: This systematic review conducted a literature search through 3 databases, following PRISMA 2020 guidelines. Inclusion criteria were written in English or Indonesian, published in 2016-2020, a randomized controlled trial (RCT) study designed using human samples, and discussed the efficacy of topical adapalene-benzoyl peroxide in mild and moderate acne vulgaris. Studies that were unavailable in full text and based on secondary data were excluded. **Results:** Acne vulgaris lesions and scars decreased significantly with adapalene/benzoyl peroxide topical therapy. The addition of moisturizer to therapy can reduce the side effects of retinoate. **Conclusion:** The combination of adapalene/benzoyl peroxide can be an alternative treatment for mild to moderate acne.

1. Introduction

Acne vulgaris (AV) is a chronic inflammation of the pilosebaceous follicles, characterized by the appearance of lesions in the form of comedones, papules, pustules, and cysts. The location of acne predilection is in areas containing sebaceous glands such as the face, neck, shoulders, upper arms, upper chest, upper back, thighs, or buttocks. AV occurs due to four main mechanisms: hyperkeratinization of follicles and pilosebaceous ducts, increased sebum production, bacterial colonization of *Cutibacterium acnes*, and inflammatory processes.[1] AV is found in 9.4% of the world's population, making AV the eighth most common disease in the world. 85% of AV patients are middle and late teens. Research conducted at Dr. M. Djamil General Hospital Padang, in 2017-2019, moderate AV degrees were experienced by patients aged 17-25 (83.3%).[3]

AV makes the patient's appearance less attractive, lowering their self-confidence and causing anxiety, depression, and even suicidal ideation.[4,5] Immediate and effective management is needed to prevent the risk of AV complications. Management of AV is determined based on severity. In mild AV, topical therapy with benzoyl peroxide, retinoids, antibiotics, or a combination. Meanwhile, a topical treatment can be combined with oral antibiotics in moderate degrees. A combination topical agent with oral isotretinoin was

recommended for severe acne vulgaris.[6]

Benzoyl peroxide (BPO) is an antibacterial agent that kills *C. acnes* by releasing free radicals. BPO also has comedolytic properties. As a therapy, BPO is available in the form of cream, gel, foam, or facial wash with a facial dose of 2.5%-10%. The limitation of BPO is its irritating effect, and it leaves a yellowish mark on the fabric. Adapalene is a retinoid derivative with selective beta and gamma receptors. Retinoids act as comedolytic and anti-inflammatory.[6]

Patient adherence to treatment is one of the keys to AV healing. Topical treatment has a lower adherence rate than oral, and the level of compliance will be lower in the use of more than one type of drug. Research shows that topical treatment using two types of combination drugs has a higher level of drug compliance than the use of two types of topical medications that are not combined.[7] This study aims to determine the effectiveness of the topical combination of adapalene and benzoyl peroxide, the dose and duration of drug use, and side effects in mild-moderate AV patients.

2. Methods

The literature search used four electronic databases: PubMed, EMBASE, and Google Scholar, from March to April 2022. The keywords used for the literature search were “acne vulgaris," “adapalene," and “benzoyl peroxide," and their synonyms were used through the MeSH term. The results were screened using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guide (Figure 1). The title of the same literature will be excluded from the search, and the research is then selected based on the title and abstract.

The inclusion criteria in this study are English or Indonesian manuscript published in 2016-2021, randomized control trials (RCT), and human studies. The exclusion criteria are unavailable full text, published other than 2016-2021, languages other than Indonesian or English, animal studies, do not use RCT design, and uses secondary data.

3. Results

From the initial search results, 234 studies were obtained from the PubMed, EMBASE, and Google Scholar databases. The initial screening excluded 54 studies with the same title. Then, based on the title and abstract, 126 unsuitable studies were reissued. Of the 54 existing research data, re-screening using inclusion and exclusion criteria, research outside of 2016-2019 35 studies, journals in languages other than Indonesian and English 3 studies, full text not available 3 studies, studies not conducted on humans 2 studies, and not a randomized controlled trial 3 studies.

Finally, there were 5 studies in this systematic review that used a regimen with a combination of adapalene and benzoyl peroxide for the treatment of acne vulgaris.

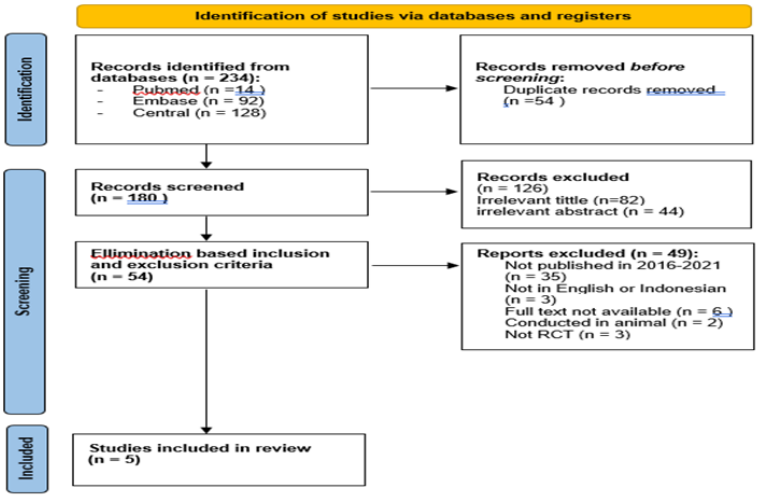

Figure 1. Systematic search process following PRISMA flow diagram 2020.

The characteristics of the study in the form of location and characteristics of the studies are shown in table 1. All studies were conducted in Canada, with 4 studies adding additional country locations, France and the USA. All studies used the RCT research method and were published in the 2016-2019 period. The characteristics of the research subjects are shown in Table 3. The subjects of this systematic review were patients with mild to moderate acne vulgaris. The distribution of the degree of acne vulgaris in these five studies used the method of Scar Global Assessment (SGA), Investigator Global Assessment (IGA), and total lesions. The first study used the SGA method and total lesions. The second and third studies used the IGA degree and total lesions, and the fourth and fifth studies used SGA, IGA, and total lesions. The number of samples from each study ranged from 45-217 people.

In these five studies, female and male research subjects were used. Research B Dreno et al. 2016, involved 63.2% more male subjects, while other studies involved 52-71% more female subjects. The age range of the study subjects varied from 12-57 years, with a mean age of 21.3 years.

Table 1. Characteristics of studies published in 2016-2019

References	Country	Study design
Dreno et al.[8]	France and Canada	Randomized control trial
Gold et al.[9]	USA and Canada	Randomized control trial
Tan et al.[10]	Canada	Randomized control trial
Dreno et al.[11]	France and Canada	Randomized control trial
Dreno et al.[12]	France and Canada	Randomized control trial

Table 2. Characteristics of patients in included studies

Authors	Age	Gender		Acne grade		
		Female	Male	SGA*	IGA†	Total lesion
Dreno et al.[8]	23.4 (20-27)	14 (36.8%)	24 (63.2%)	Mild or moderate 81.1%	-	25.0 (12.9)
Gold et al.[9]	20.1 (12-57)	113 (52.1%)	104 (47.9%)	-	Mild or moderate 51.2%	98.5
Tan et al.[10]	20 (14-26)	71 (57.7%)	52 (42.3%)		Mild or moderate 100%	51-62.5
Dreno et al.[11]	21.5 ± 4.2	44 (65.7%)	23 (34.3%)	Mild or moderate 82.6%	Mild or moderate 92.5%	39.8 ± 13.7
Dreno et al.[12]	21.8 (16-35)	32 (71.1%)	13 (28.9%)	Mild or moderate 88.9%	Mild or moderate 93.3%	38.9 (15-69)

*Scar Global Assessment; † Investigator Global Assessment.

Table 3. Findings from each included studies

References	Regiment	Result
Gold et al.[9]	0.3 % A/BPO for 12 weeks	1. Topical combination 0.3% A/BPO was 30% more efficient than placebo after 12 weeks (p < 0.001) 2. Topical combination 0.1% A/BPO was 8.7% more efficient than placebo after 12 weeks (p < 0.443) 3. 0.3% A/BPO was well tolerated, almost the same as 0.1% A/BPO with complaints of mild irritation (2.8% of subjects), and burning sensation (0.9% of subjects) 4. The results of subject satisfaction showed twice as much better for the combination of 0.3% A/BPO compared to placebo.
	0.1% A/BPO for 12 weeks	
	Placebo for 12 weeks	
Dreno et al. [8]	Adapalene 0,1%/benzoyl peroxide 2,5% in split face for 24 weeks	1. Use of A/BPO for 24 weeks can reduce the risk of new atrophic scar formation. The scar on the use of A/BPO was 4.5%, while on the placebo side, it was 24.8%. 2. Group A/BPO achieved "almost clear" SGA increased from 9.7% at the start of the study to 45.2% at week 24 3. A/BPO decreased the number of lesions within 6 months of observation (p<0.05). Mean inflammatory lesions decreased by 72%, and non-inflammatory lesions decreased by 58% from study entry to week 24. Total lesions decreased by 65% on A/BPO treatment compared to 36% placebo. 4. Side effects found in the form of skin irritation 42%, erythema and burning sensation 10.5%, and flaky 2.6%.
Tan et al.[10]	0,1% % A/BPO 3 hours/day for 12 weeks	1. A/BPO everyday group showed that the complaints of burning sensation were mild than the use of A/BPO every day (p<0.05) 2. A/BPO everyday group complained of a more flaky effect than the A/BPO use every day (p<0.05) and the A/BPO with moisturizer (p<0.01) 3. Complaints of redness are almost found in all groups using the A/BPO regimen, only slightly better when using A/BPO at intervals 4. The A/BPO regimen showed efficacy in reducing the number of lesions in all groups, with a mean of -64% with 3-hour A/BPO, -61% with moisturizing A/BPO, -67% with day-interval A/BPO, and -66 % on A/BPO every day after 12 weeks of use.
	0,1 % A/BPO and moisturizer for 12 weeks	
	0,1 % A/BPO every other night	
	0,1 % A/BPO night	
Dreno et al.[11]	Adapalene 0,3%/Benzoyl Peroxide 2,5% in the split face with additional cleanser twice a day and moisturizer in the morning for 24 weeks	1. Atrophic scars decreased at week 24 by 15.5% in the A/BPO preparation compared to placebo. Atrophic scars increased by 14.4% 2. Acne lesions decreased more at the site given A/BPO than placebo. The decrease in total lesions was 73%, inflammatory lesions 86.7%, and non-inflammatory lesions 59.5% on A/BPO administration. While the placebo decreased total lesions by 50.9%, 57.9% for inflammatory lesions, and 41% for non-inflammatory lesions. 3. Global improvement in acne was found to be greater with A/BPO administration of 64.2% compared to 19.4% for placebo. 4. The side effects found were irritation (14% BPO, 6% placebo) and facial skin pain (3% A/BPO, 1.5% placebo).
Dreno et al.[12]	Continuing giving adapalene 0,3%/benzoyl peroxide 2,5% full face with additional cleanser twice a day and moisturizer in the morning for 24 weeks (total 42 weeks)	1. On the side of the face using A/BPO at 24 weeks reduced scars by 21.7%, and at 48 weeks, they decreased by 26.9%. While on the side of the face that used a placebo in the first 24 weeks, the scar increased by 16.7%, but the size at 48 weeks was 22.7%. 2. A/BPO 0.3%/2.5% for 48 weeks on one side of the face was more effective in cleaning and reducing the number of scars compared to the other side of the face that received 24 weeks of therapy with an average number of scars of 8.4 at 48 weeks of therapy and 9.9 on the other side of the face. 24 weeks of therapy (p=0.0185) 3. Side effects were found in 6 subjects (13.3%), but side effects were more tolerable in stage 2 than in stage.

Notes: BPO (benzoyl peroxide); A/BPO (adapalene/benzoyl peroxide).

4. Discussion

From the table above, it can be seen that research from 2016-2020 showed that topical adapalene and benzoyl peroxide were effective in reducing the degree of acne vulgaris. In the study of Dreno et al.[8] was given a topical regimen of adapalene 0.1%/benzyl peroxide 2.5% and placebo once daily on a split face and evaluated at 24 weeks. Observations were made every 2 weeks from the second to the sixth month. Topical therapy A 0.1/BPO 2.5 reduced the number of lesions better than placebo ($p<0.005$), inflammatory lesions decreased 72%, non-inflammatory lesions decreased 58%, and total lesions decreased 65% from the start of the study. The use of placebo also reduced total lesions by 36%, but the number of atrophic scars was higher in placebo at 24.8% compared to A 0.1/BPO 2.5 4.5%. So in this study, it was concluded that using A 0.1/BPO 2.5 can also reduce the risk of atrophic scar formation.[8]

In the second study by Gold et al., the USA and Canada were given 3 different regimens for 12 weeks. The first regimen was A 0.1/BPO in 217 subjects, A 0.3/BPO in 217, and placebo in 69 subjects. The results obtained that combination A 0.3/BPO was 30% more efficient than placebo ($p<0.001$), and combination A 0.3/BPO was 8.7% more efficient ($p<0.443$) than placebo.[9]

The third study by Jerry Tan et al. used 4 different groups: A 0.1/BPO for 3 hours a day, A0.1/BPO using a moisturizer, A 0.1/BPO every day, and A 0.1/BPO every night. All A/BPO regimens showed good effectiveness in reducing the number of acne vulgaris lesions. The mean decrease in the number of lesions was 64% in the 3-hour A/BPO group, 61% decrease with moisturizing A/BPO, 67% decrease in day-interval A/BPO, and 66% decrease in daily A/BPO. More significant results were obtained in the A/BPO group with moisturizer because the side effects, such as dry skin, burning sensation, and flacking skin, were less than in the daily A/BPO regimen ($p<0.06$).[10]

The fourth and fifth studies by Dreno et al. which was carried out in 2018 with the split face method and continued on the entire face in 2019. The regimen used A0.3/BPO, and a placebo was given once a day. Besides that, facial cleansers were also given twice a day and moisturizer in the morning for 6 months. The results showed that acne lesions decreased by 73% on the A/BPO-treated side compared to 50.9% on the placebo. The decrease in SGA was found to be greater in A/BPO, 64.2%, compared to 19.4% for placebo. On the entire side of the face, A/BPO found a decrease in facial lesions at 48 weeks of 86.7% compared to the side of the face using 24 weeks of 78.9% ($p<0.0125$).[11,12]

Of the five analyzed studies, the same results were obtained. Topical administration of A/BPO reduced total lesions by 60-73%, inflammatory lesions by 58-86%, and non-inflammatory lesions by 41-58% in mild to moderate acne vulgaris patients. While the group that was given a placebo reduced the total lesions by 36%. Although acne vulgaris is of self-limiting disease, there is a risk of causing permanent scars that reduce the patient's confidence. Giving A/BPO can reduce the risk of new scars and eliminate existing scars.[13-17] In the research conducted by Dreno et al., it was found that the use of A0.1/BPO could reduce scars by 4.5% and did not cause new atrophic scars, while the placebo increased atrophic scars by 24.8%. In 2018, retinoids were given back on one side of the face with a larger dose of A0.3/BPO plus moisturizer for 24 weeks. The results obtained A 0.3/BPO reduced atrophic scars by 15.5% compared to placebo, which increased atrophic scars by 14.4%. The study was resumed in 2019 by administering A0.3/BPO and moisturizer on the entire face for 24 weeks using the same patient in the previous year. Results showed that using A0.3/BPO for 48 weeks reduced scars by 26.9%, while on the side of the face, the use of 24 weeks reduced scars by 21.7%.

Research conducted by Tan et al. compared the method of giving A0.1/BPO by dividing into 4 groups, namely A/BPO using for 3 hours, A/BPO using a moisturizer, A/BPO every day, and A/BPO every day. Results obtained A/BPO effectively reduced lesions in all groups, with an average of -64% with A/BPO 3 hours, -61% with A/BPO moisturizer, and -67% with

A/BPO at intervals of days and -66 % on A/BPO daily after 12 weeks of use. In addition, giving a moisturizer can relieve the side effects of retinoids in the form of complaints of dry skin, redness, burning sensation, and flaky skin. A/BPO with moisturizer.[10]

5. Conclusion

Adding moisturizers along with A/BPO can reduce the risk of atrophic scar formation and the side effects of using retinoids. The dosages that have been approved by the Food and Drugs Administration (FDA) are adapalene 0.1%/benzoyl peroxide 2.5% for >9 years of age and adapalene 0.3%/benzoyl peroxide 2.5% for >12 years of age. Larger doses of adapalene with moisturizer reduced total lesions and scars more effectively.

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