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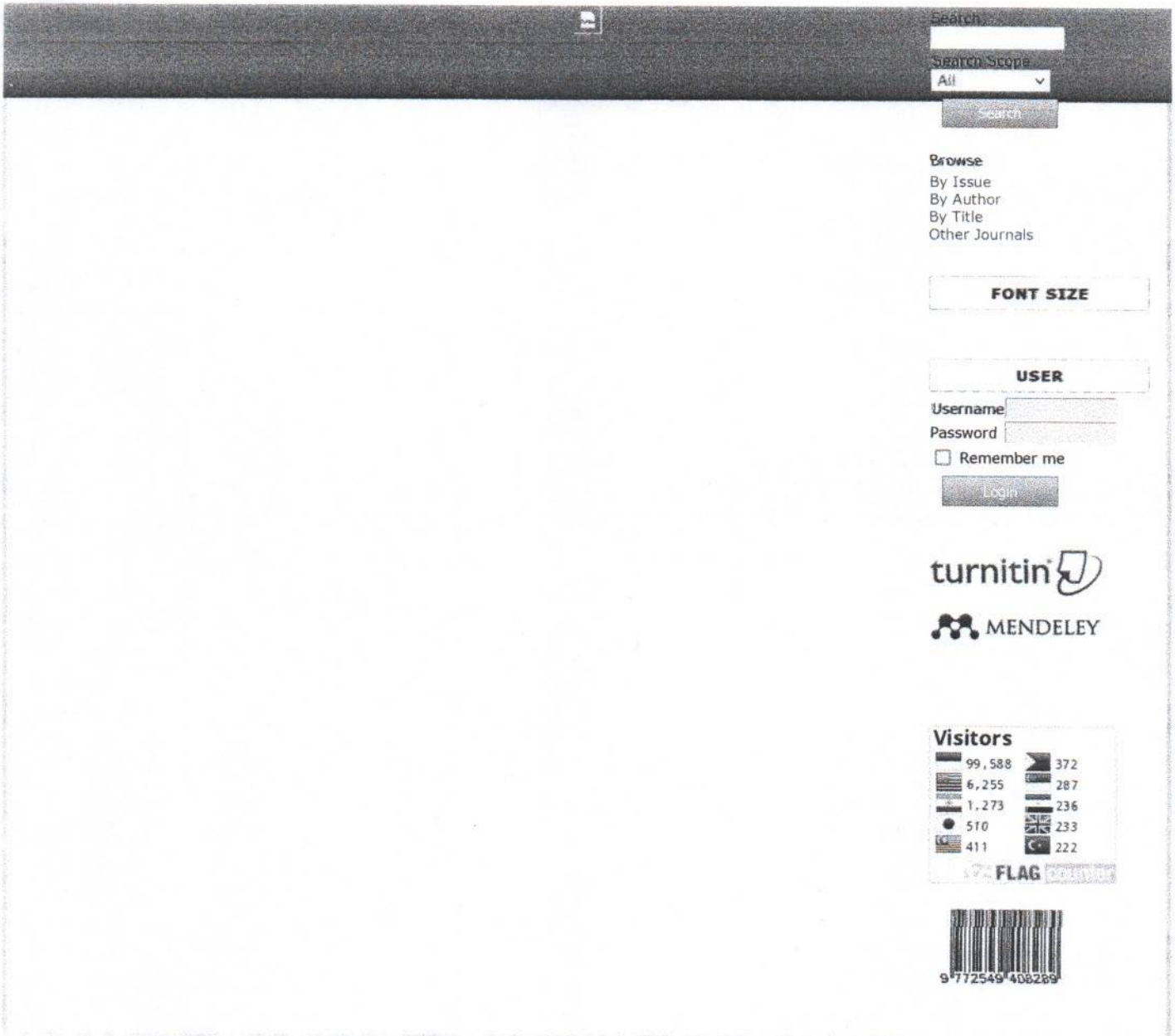
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Berkala Ilmu Kesehatan Kulit Dan Kelamin

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Comparison of the Efficacy of Topical Clindamycin versus Niacinamide in the Treatment of Mild to Moderate Acne Vulgaris: a Systematic Review

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ABSTRACT

Background: Acne vulgaris (AV) is one of the most common skin diseases among teenagers and is treated based on its severity. Mild acne is treated with topical agents, while moderate and severe acne are treated with a combination of topical and systemic agents. Topical agents that are often used for acne are antibiotics, such as topical clindamycin. Widespread use of antibiotics to treat AV causes resistance problems. Therefore, alternative therapies are needed to prevent resistance to topical clindamycin, such as topical niacinamide, which has anti-inflammatory effects without inducing resistance problems. **Purpose:** To compare the efficacy of topical clindamycin and topical niacinamide in mild to moderate AV. **Methods:** In this systematic review, a literature search was carried out through 6 databases, following PRISMA 2020 guidelines. Inclusion criteria were written in English or Indonesian, published in 2010-2020, randomized controlled trial (RCT) study design, conducted on human samples, and discussed the efficacy comparison of topical clindamycin and niacinamide in mild to moderate AV. Studies that were not accessible in full-text and based on secondary data were excluded. Quality and risk of bias assessments were done using The Jadad Scale and Risk of Bias 2 (RoB 2). **Result:** Acne severity was reduced significantly in both topical clindamycin and niacinamide groups, and there was no efficacy difference between these groups. Both topical clindamycin and topical niacinamide can cause mild side effects. **Conclusion:** Topical niacinamide can be an alternative therapy to topical clindamycin because they are both effective in treating mild to moderate AV.

Keywords: acne vulgaris, skin disease, clindamycin, niacinamide, health education.

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BACKGROUND

Acne vulgaris (AV) or commonly referred to acne, is a chronic skin disease that occurs due to obstruction of hair follicles by dead skin cells and sebum and is characterized by the presence of comedones, pimples, oily skin, and scars.[1,2] This multifaceted skin disease can be caused by hyperplasia of the sebaceous glands, microbial colonization, abnormal follicular differentiation with increased keratinization, and increased inflammation.[1,3] AV is experienced by about 75% of teenagers in the world, who are generally aged 12-15 years old. The severity peak is at the age of 17-21.[4] A study conducted in the Cosmetic Medical Division of Dermatology and Venereology Outpatient Unit at Dr. Soetomo General Academic Hospital Surabaya stated that from May to August 2015, the highest number of AV patients aged 15-19 years old (52.4%).[5]

AV is a self-limiting disease.[3] However, a study stated that acne was considered a problem and caused sufferers to become dissatisfied with their appearance and resulted in a lack of self-confidence.[6] Therefore, AV patients must get the right treatment. Management of AV is determined based on its severity.[7] Mild AV is treated with topical agents, while moderate and severe AV are treated with a combination of topical agents and systemic agents.[8] One of the topical agents used in the management of AV is antibiotics. The most commonly used topical antibiotics for AV are erythromycin and clindamycin.[3] Continuous use of antibiotics in the management of AV can cause resistance to *Propionibacterium acnes* (*P. acnes*).[9,10] In 2016, genomic and metagenomic investigations were conducted and led to a change in the denomination of *P. acnes* to *Cutibacterium acnes* (*C. acnes*).[11]

In 2009 in Hong Kong, 54.7% of 47 AV strains studied from AV patients carried *C. acnes* strains resistant to at least one antibiotic. Strains resistant to clindamycin ranked first (53.5%), followed by those resistant to erythromycin (20.9%).[10] This resistance is

one of the causes of failure in AV therapy. Therefore, it is necessary to develop alternative therapies that provide therapeutic characteristics of antimicrobial agents without causing the problem of resistance to bacteria.[9]

One of the antibiotics that often causes this resistance is topical clindamycin. Clindamycin works by binding to the 50s subunit of bacterial ribosomes and suppressing protein synthesis, thus providing an antibacterial effect. Clindamycin also has anti-inflammatory properties to inhibit the inflammatory response induced by *C. acnes*.[12] Several studies have tried to prove that topical niacinamide (also known as nicotinamide) can be used as an alternative therapy in AV patients because niacinamide also has strong anti-inflammatory properties and has been used in various inflammatory skin diseases, both topically and systematically. Niacinamide, which is also known as Nicotinamide, works by providing potent anti-inflammatory properties without inducing bacterial resistance.[9] However, until now, there have been few studies that provide data and describe this. This study aims to examine previous studies which discussed the comparison of the effectiveness of topical clindamycin with topical niacinamide in patients with AV grade mild to moderate. Hopefully, this research can be the basis for determining the management of AV in the future.

METHODS

This was a systematic review aimed to compare the efficacy of topical clindamycin and topical niacinamide in mild to moderate AV. A literature search was carried out through 6 databases: *Springer Link, Scopus, ScienceDirect, ProQuest, PubMed,* and *Cochrane* from February to March 2021. Search terms used in this study were acne vulgaris, topical clindamycin, topical niacinamide, and their synonyms. Studies identified from the literature search were then screened following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Figure 1). Duplicates were removed after the initial search. Then these studies were screened based on their titles and abstracts.

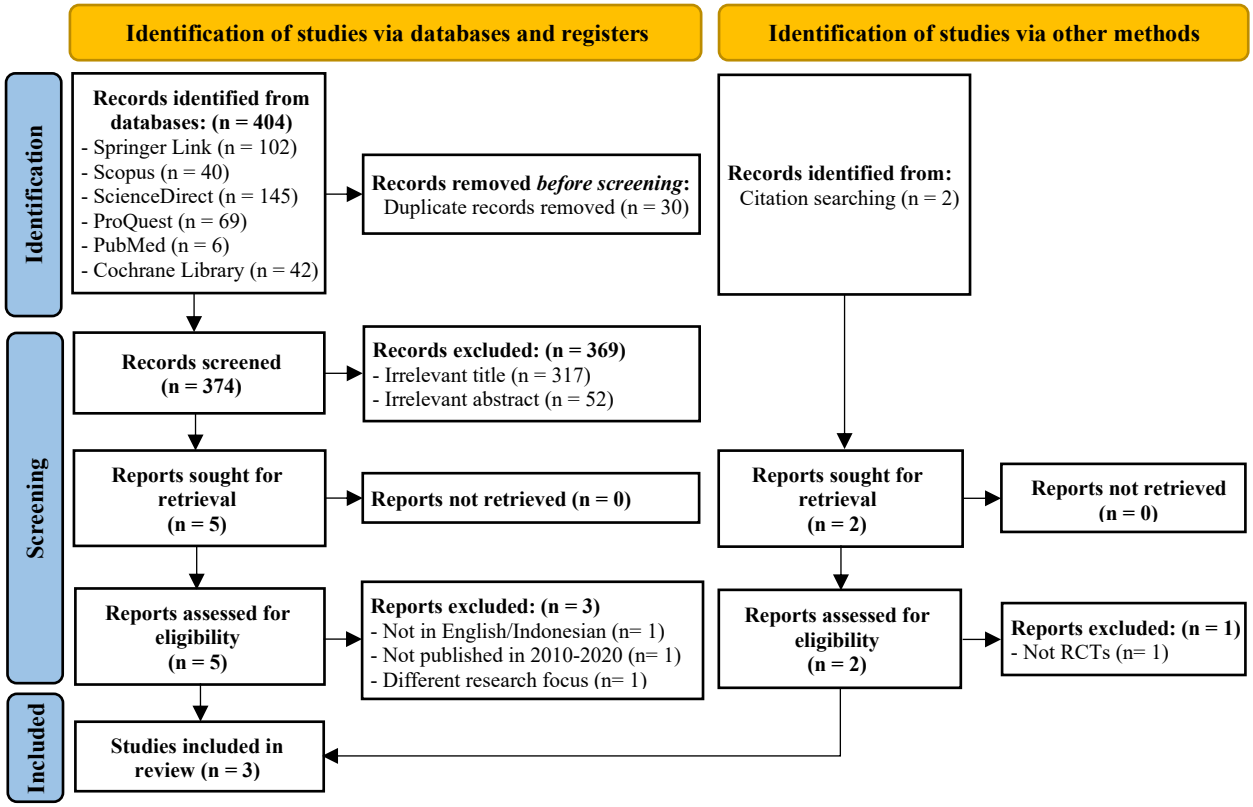

Figure 1. Systematic search process following PRISMA flow diagram 2020.

Furthermore, the full-texts of each study were assessed to determine which studies would be included in this systematic review. The inclusion criteria were English or Indonesian language, published in 2010-2020, Randomized Controlled Trials (RCTs) study design, conducted on human samples, and discussed the efficacy comparison of topical clindamycin versus topical niacinamide therapy in patients with AV grade mild to moderate. Studies that were not accessible in full-text and based on secondary data were excluded.

The Jadad Scale and the Revised Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials were then

used to assess the quality and risk of bias of the included studies. The results of quality assessment by using the Jadad Scale were that two studies got a total score of 4, and one study got a total score of 3. So all of these studies have good quality (≥3). Meanwhile, the results of risk of bias assessment with RoB 2 found that one study had a low risk of bias and two studies had an unclear risk of bias.

Table 1. Quality Assessment by Using Jadad Scale

Study Author	Randomization	Blinding	Withdrawals and Dropouts	Total Score
Shahmoradi *et al.*[13]	1	2	1	4/5
Nugroho & Widayati[14]	0	2	1	3/5
Khodaeiani *et al.*[15]	1	2	1	4/5

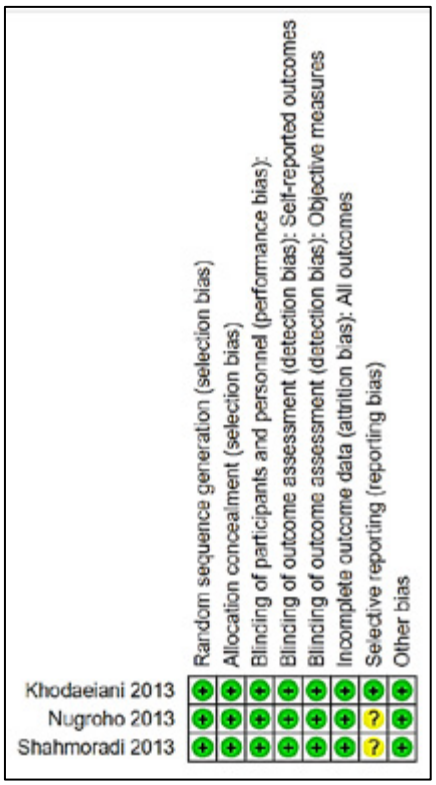

Figure 2. Risk of Bias Assessment by Using Risk of Bias 2 (RoB 2).

Following that, the data extraction was completed. Following that, the data extraction was completed. Data from included studies were collected and consisted of the first author's, year of publication, study design, country of study, characteristics of research subjects (including patient demographics and baseline acne grade), acne grading system, topical clindamycin or niacinamide topical therapy regimen, and patients' outcomes.

RESULT

From the initial search, 406 studies were identified. After 30 duplicates were removed, 376 studies were screened. The results were that 369 studies were excluded based on the titles and abstracts, and four studies were excluded based on full-text assessments for eligibility. Finally, three studies were included in this systematic review. The three studies included in this systematic review were designed to compare the efficacy of topical clindamycin and topical niacinamide in mild to moderate AV.

The characteristics of each included study are shown in Table 2. Two studies were conducted in Iran and one study was conducted in Indonesia. These included studies that were published in 2013 and used RCT study design.

The characteristics of patients in the included studies are shown in Table 3. The studies included in this systematic review were studies in patients with mild to moderate grades of AV. The determination of AV grades in these three studies used different methods. The first study used the Acne Severity Index (ASI). The second one only counted the number of acne lesions. The third one used three different grading methods: The Leeds Acne Grading Technique, counted the total number of facial papules or pustules, and Cook's grading scale. The sample size among the included studies varies from 40 to 60 people.

In the study conducted by Shahmoradi *et al.*[13], all of the research subjects were females. Meanwhile, in the research conducted by Nugroho and Widayati[14] and Khodaeiani *et al.*[15], the research subjects consisted of males and females. The range of age of the patients in all of these studies was approximately the same. There were no significant demographic differences between the two treatment groups.

Table 2. Characteristics of the Included Studies Published in the Period 2010-2020

References	Country	Study Design
Shahmoradi *et al.*, 2013[13]	Iran	Double-blind, randomized controlled clinical trial
Nugroho & Widayati, 2013[14]	Indonesia	Double-blind, randomized controlled trial
Khodaeiani *et al.,* 2013[15]	Iran	Double-blind, randomized clinical trial

Table 3. Characteristics of the Patients in Included Studies

Study Author (Year)	Age		Sex		Baseline Acne Grade		Exclusion Criteria
	Topical Clindamycin Group	Topical Niacinamide Group	Topical Clindamycin Group	Topical Niacinamide Group	Topical Clindamycin Group	Topical Niacinamide Group	
Shahmoradi *et al.,* (2013)[13]	20.83 ± 3.34 (mean, SD)	21.17 ± 3.53 (mean, SD)	Female [n = 30] (50%)	Female [n = 30] (50%)	Mild or moderate: •ASI = 18.2 ± 12.27 (mean, SD)	Mild or moderate: • ASI = 16.85 ± 8.5 (mean, SD)	•Pregnant and breastfeeding or use oral contraceptive pill (OCP) •Received topical/oral medication for AV in the last 1 month •History of clindamycin/nicotinamide allergy, as well as renal, hepatic, or endocrine issues
Nugroho & Widayati, (2013)[14]	18-25 (range)	18-25 (range)	Male [n = 10] (25%) & Female [n = 10] (25%)	Male [n = 10] (25%) & Female [n = 10] (25%)	Mild to moderate: •Total lesion = 3.75 ± 1.410 (mean, SD)	Mild to moderate: •Total lesion = 3.00 ± 2.471 (mean, SD)	•Menstruating •Pregnant or breastfeeding •Use hormonal contraceptive •Received topical medication for acne or topical corticosteroid in the last 2 weeks •Currently receiving systemic antibiotic or steroid therapy
Khodaeiani *et al.,* (2013)[15]	23.25 ± 3.77 [18.00-31.00] (mean, SD, %)	23.88 ± 3.67 [18.00-30.00] (mean, SD, %)	Male [n = 13] (16.25%) & Female [n = 27] (33.75%)	Male [n = 15] (18.75%) & Female [n = 25] (31.25%)	Moderate: •*Leeds technique* : Grade III •Number of facial papules or pustules: 88.20 ± 3.44 (mean, SD) •*Cook's grading*: 5.70 ± 0.94 (mean, SD)	Moderate: •*Leeds technique* : Grade III •Number of facial papules or pustules: 87.98 ± 3.17 (mean, SD) •*Cook's grading*: 5.93 ± 0.83 (mean, SD)	•Pregnant, breastfeeding, or intend to become pregnant •Undergone any other acne treatment or using any interaction medicine in the preceding 3 months •Received oral isotretinoin therapy during the past year •Acne due to secondary causes •Another dermatological face disease •Significant systemic diseases such as colitis •Known hypersensitivity to study medications

Description: SD: Standard Deviation; ASI: Acne Severity Index; OCP: Oral contraceptive pill; AV: Acne vulgaris.

Table 4. Findings from Each Included Studies

Study Author (Year)	Regimen		Findings
	Topical Clindamycin Group	Topical Niacinamide Group	
Shahmoradi *et al.* (2013)[13]	2% clindamycin gel (twice daily for 8 weeks, evaluated every 2 weeks)	5% niacinamide gel (twice daily for 8 weeks, evaluated every 2 weeks)	• Topical clindamycin and topical niacinamide were both effective in treating mild to moderate AV. • Mean of ASI at baseline in the clindamycin group (18.2 ± 12.27) and niacinamide group (16.85 ± 8.5) had no significant difference ($p > 0.05$). • Mean of ASI in the clindamycin group and niacinamide group experienced a significant decrease compared to baseline ($p < 0.0001$), but there was no significant difference in ASI reduction between these groups ($p = 0.583$). • No side effects were observed during treatment.
Nugroho & Widayati, (2013)[14]	1% clindamycin gel (twice daily for 2 weeks, evaluated after 2 weeks)	niacinamide + zinc gel (twice daily for 2 weeks, evaluated after 2 weeks)	• Topical clindamycin and topical niacinamide + zinc were both effective in reducing the number of acne lesions. • Mean number of acne lesions at baseline in the clindamycin group (3.75 ± 1.410) and niacinamide + zinc group (3.00 ± 2.471) had no significant difference ($p = 0.248$). • Number of lesions after treatment in clindamycin group (1.25 ± 0.910) and niacinamide + zinc (1.40 ± 2.113) decreased significantly ($p = 0.000$; $p = 0.008$). • Recovery proportion in the clindamycin group was 69%, while in the niacinamide + zinc group was 64%. Therefore, there was no significant difference between these groups ($p = 0.620$).
Khodaeiani *et al.,* (2013)[15]	1% clindamycin gel (twice daily for 8 weeks, evaluated every 4 weeks)	4% niacinamide gel(twice daily for 8 weeks, evaluated every 4 weeks)	• Topical clindamycin and topical niacinamide were both effective in treating acne vulgaris. • Mean number of papules or pustules at baseline in the clindamycin group (88.20 ± 3.44) and niacinamide group (87.98 ± 3.17) had no significant difference ($p = 074$), as well as the baseline of acne grade in clindamycin group (5.70 ± 0.94) and niacinamide group (5.93 ± 0.83) had no significant difference ($p = 0.20$). • Grade of acne at the end of the study was decreased significantly in both groups compared to baseline ($p < 0.001$), but there was no significant difference in reduction of the number of facial papules/pustules between these groups ($p > 0.05$). • There were no serious side effects experienced by the patients. Side effects were minor (including itching, burning, crusting, greasiness, and contact dermatitis) were experienced by 11 (27.5%) patients in clindamycin group and (35%) patients in niacinamide group

Description: AV: Acne vulgaris; ASI: Acne Severity Index.

From Table 4 above, it can be seen that research conducted from 2009 to 2010 at St-Alzahra Hospital showed that both 2% clindamycin gel and 5% niacinamide gel were effective in reducing the grade of AV. At baseline, mean ASI in both groups had no significant difference, which was 18.2 ± 12.27 in the clindamycin group and 16.85 ± 8.5 in the niacinamide group. Furthermore, after giving 2% clindamycin gel

and 5% niacinamide gel twice daily in each treatment group for 8 weeks and then evaluating every 2 weeks at 2, 4, 6, and 8 weeks, the mean of ASI decreased significantly compared to baseline ($p < 0.0001$). There was no significant difference regarding the decrease of ASI in either of the two groups ($p = 0.583$). At week 8, both the clindamycin and niacinamide groups had the highest percentage of ASI reduction, at 77.32% and 87.72%, respectively.[13]

The same result was also revealed by a study conducted in 2013 at the Faculty of Medicine, Universitas Diponegoro, which stated that both 1% clindamycin gel and niacinamide + zinc gel were equally effective for reducing the total number of acne lesions, although the composition was slightly different. In this study, the mean of total acne lesions before treatment between the two groups had no significant difference, which was 3.75 ± 1.410 in the clindamycin group and 3.00 ± 2.471 in the niacinamide + zinc group. Both groups were then treated with 1% clindamycin gel and niacinamide + zinc twice daily for 2 weeks and evaluated after 2 weeks. The result showed a significant decrease in total acne lesions in the clindamycin group ($p = 0.000$) and the niacinamide + zinc group ($p = 0.008$). Thus, the mean recovery proportion in the clindamycin group was 69%, with all study subjects experiencing a decrease in total acne lesions and 25% of them experiencing a 100% cure. In the niacinamide + zinc group, the mean recovery proportion was slightly lower at 64.20%, of which 40% were 100% cured, while the other 10% had no reduction at all in the numbers of acne.[14]

Those findings were also supported by Khodaeiani *et al.* in their study, which stated that the effectiveness of topical clindamycin and topical niacinamide had no significant difference. There was no significant difference in the severity of acne between the two treatment groups before receiving treatment, either in the mean number of papules or pustules ($p = 0.74$) or the mean acne grade ($p = 0.20$). After administration of 1% clindamycin gel and 4% niacinamide gel twice daily in each group for 8 weeks and then evaluated every 4 weeks at weeks 4 and 8, acne grade decreased significantly ($p < 0.001$). However, there was no significant difference in the reduction of acne grade in the two groups ($p > 0.05$). The largest percentage decrease in the number of papules or pustules in both groups occurred at week 4, from 78.00-95.00% to 39.00-58.00% in the clindamycin group and from 82.00-95.00% to 43.00-60.00% in the niacinamide group.[15]

For AV patients who tolerated the treatment well, administration of topical clindamycin and topical niacinamide did not cause any side effects.[13] However, some patients could experience mild side effects. After topical administration of clindamycin gel, 27.5% of 40 patients experienced mild side effects, including itching (7.5%), crusting (7.5%), greasiness (7.5%), and burning (5%). Likewise, after administration of nicotinamide gel, 35% of 40 patients experienced mild side effects, including burning (17.5%), itching (10%), crusting (5%), and mild dermatitis (2.5%).[15]

DISCUSSION

This systematic review aimed to explain the effectiveness of topical clindamycin compared to topical niacinamide in treating AV and to determine if topical niacinamide can be used as an alternative therapy to topical clindamycin in the treatment of AV. The results extracted from the 3 included studies in this review showed the same results that topical clindamycin and topical niacinamide did not have a significant difference in effectiveness. Almost all AV patients who were given 1-2% clindamycin gel and 4-5% niacinamide gel or niacinamide + zinc gel for 2-8 weeks experienced a significant reduction in acne grade.[13–15] Only some of the patients experienced no acne lesion reduction at all.[14]

When compared, the percentage of cure in the clindamycin group and the niacinamide group had no significant difference. A study conducted by Nugroho and Widayati showed that the mean cure percentage in the clindamycin group (69%) was slightly higher than the nicotinamide + zinc group (64.2%).[14] This finding is also supported by a study by Khodaiani *et al.* who found that the cure percentage in the clindamycin group (75%) was higher than the niacinamide group (72.5%).[15] Because niacinamide + zinc does not have antibacterial activities like clindamycin, but instead has anti-inflammatory effects, it can only suppress inflammation.[14] Overall, there was no significant difference in the cure percentage between the two groups.

Regarding the role of zinc in one of the included studies, the review stated that zinc was equally as effective or more effective than clindamycin.[16] Another study also found that topical clindamycin + zinc twice daily and topical clindamycin alone twice daily had a therapeutic similarity.[17] This proved that the addition of zinc has no significant effect on the efficacy or effectiveness of topical niacinamide therapy in AV patients.

Interestingly, one of the three included studies also stratified the changes in the mean grades of facial acne based on the patients' skin type. It was stated that the best reduction in acne grade was experienced by the non-oily skin group treated with clindamycin, followed by the oily-skin group treated with niacinamide, the

oily skin group treated with clindamycin, and the non-oily skin group treated with niacinamide ($p < 0.001$). However, the possibility of an association between skin type and the effectiveness of topical therapy in AV patients was not supported by clinical evidence.[15]

Side effects were also found after the administration of topical clindamycin and topical niacinamide. One of the included studies reported mild side effects experienced by 11 (27.5%) patients who received 1% clindamycin gel and 14 (35%) patients who received 4% niacinamide gel. These side effects include itching, burning, crusting, greasiness, and mild dermatitis.[15] The other study reported that the treatment was tolerated very well by all the AV patients and that there were no side effects observed during the treatment.[13] This proved that after the use of topical clindamycin and topical niacinamide, AV patients could experience mild side effects or did not experience side effects at all. These results are consistent with the previous study.[9]

This systematic review found that both topical clindamycin and topical niacinamide were equally effective in reducing the severity or treating mild to moderate AV. No significant efficacy difference between these two therapies were found. Thus, topical niacinamide can be considered as an alternative therapy to topical clindamycin in treating mild to moderate AV. However, not all AV patients respond well to this treatment. Some patients with mild to moderate grades of acne may experience mild side effects including itching, burning, crusting, greasiness, and contact dermatitis.[15]

This systematic review has several limitations that must be considered. First, only studies available in Indonesian or English were included, so it may not be all eligible and relevant literature to be reviewed. Second, inclusion criteria of AV patients in each included study were slightly different, and the demographic characteristics of AV patients in each included study were heterogeneous, which could affect the results of this review. Third, the treatments given to both groups in all included studies were not the same in terms of dose and duration of administration. Fourth, differences in the country where the research was conducted could affect the results of this study. Fifth, the acne grading systems used by each included study were all different so that the category of mild or moderate AV may vary slightly between studies.

Moreover, further research with RCT study design on a larger scale and more detail in the inclusion criteria of the samples is needed to prove the effectiveness of topical niacinamide as an alternative therapy for topical clindamycin in mild to moderate AV, and also to provide a more generalized context for this systematic review.

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