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The efficacy of combination of oral antioxidants and topical retinoic acid versus topical retinoic acid monotherapy in mild acne vulgaris patients

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ABSTRACT

Acne vulgaris (AV) is a chronic inflammatory disorder of the pilosebaceous follicle with multifactorial pathogenesis and pleiomorphic clinical manifestations constituting comedones, papules, pustules, nodules, and cysts. Oxidative stress has been reported to contribute in AV pathogenesis. This phenomenon rationalizes antioxidant supplementation as an adjuvant therapy for AV management. Four cases of 22 to 23 yo women with complaints of worsening facial acne for 1 to 6 mo. Initially, acne lesions appeared as skin-colored papules, which increased in number, became reddish papules and pustules, and extended to the jaw and chin. Lesions were accompanied by temporary itching and pain. Dermatological examination revealed multiple circumscribed discrete erythematous papules, miliar to lenticular in size, comedones (+), and pustules (+), with total lesions <30. According to the Lehmann criteria, patients were diagnosed as mild AV. All patients were treated with 0.025% topical retinoic acid cream, while the other two patients received additional oral antioxidant supplementations (zinc and α-lipoic acid) and were followed up every two weeks. Two cases who received additional oral antioxidant supplementations (Group A) exhibited an earlier and higher clinical improvement, characterized by a reduction in the number of lesions on each follow up, till the current report. Oxidative stress in AV pathogenesis causes microenvironment alteration that favours colonization of *Cutibacterium acnes*. Together with the increase in sebum production, it stimulates the release of pro-inflammatory cytokines, such as interleukin (IL)-1α, IL-8, and tumor necrosis factor-α (TNF α), contributing to the inflammatory response. Antioxidant supplementation plays a role in suppressing the process of lipid peroxidation and inhibiting the expression of pro-inflammatory cytokines. Comprehensive management of AV is based on pathogenesis and the role of oxidative stress. An earlier and higher clinical improvement reduction was noted in Group A, patients who received a combination of 0.025% topical retinoic acid cream and oral antioxidant supplementation.

ABSTRACT

Akne vulgaris (AV) adalah gangguan inflamasi kronis pada folikel pilosebasea dengan patogenesis multifaktorial dan manifestasi klinis pleiomorfik yang terdiri dari komedo, papul, pustul, nodul, dan kista. Stres oksidatif telah dilaporkan berkontribusi dalam patogenesis AV. Fenoma ini merasionalisasi suplementasi antioksidan sebagai terapi adjuvan untuk tatalaksana AV. Empat kasus wanita berusia 22 hingga 23 tahun dengan keluhan jerawat wajah yang memburuk selama 1 - 6 bulan. Awalnya, lesi jerawat muncul sebagai papul sewarna kulit yang bertambah jumlah, menjadi papul kemerahan dan pustul, serta meluas ke rahang dan dagu. Lesi disertai dengan rasa gatal dan nyeri hilang timbul. Pemeriksaan dermatologis menunjukkan papul eritematosa multipel, ukuran miliar-lentikular, komedo (+), dan pustul (+), dengan total lesi <30. Berdasarkan kriteria Lehmann, pasien didiagnosis sebagai AV ringan. Semua pasien diberikan terapi topikal asam retinoat 0.025%, dengan dua pasien mendapatkan tambahan suplementasi antioksidan oral (zink dan asam α-lipoat) dan ditindak lanjuti setiap 2 minggu. Dua kasus yang mendapatkan suplementasi antioksidan oral (Grup A) menunjukkan perbaikan klinis yang lebih awal dan lebih tinggi, ditandai dengan penurunan jumlah lesi pada setiap tindak lanjut, hingga penulisan saat ini. Stres oksidatif pada pathogenesis AV menyebabkan perubahan lingkungan mikro yang mendukung kolonisasi *Cutibacterium acnes*. Bersama dengan peningkatan produksi sebum, hal ini menstimulasi pelepasan sitokin pro-inflamasi, seperti interleukin (IL)-1α, IL-8, dan tumor necrosis factor-α (TNFα), yang berkontribusi pada respon inflamasi. Suplementasi antioksidan berperan dalam menekan proses peroksidasi lipid dan menghambat ekspresi sitokin proinflamasi. Penatalaksanaan AV yang komprehensif didasarkan dari patogenesis dan peran stres oksidatif. Perbaikan klinis yang lebih awal dan lebih tinggi terlihat pada Grup A, pasien yang menerima kombinasi topikal asam retinoat 0.025% dan suplementasi antioksidan oral.

Keywords:
acne vulgaris;
α-lipoic acid;
antioxidant;
oxidative stress;
zinc

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INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory disorder of the pilosebaceous unit with multifactorial pathogenesis and pleiomorphic clinical manifestations comprising comedones, papules, nodules, and cysts.[1] It is a prevalent dermatological disorder primarily affecting adolescents and young adults, with an estimated incidence of ~85%.[2] Acne vulgaris has a complex pathogenesis constituting 1) follicular epidermal hyperproliferation, 2) increased sebum production, 3) colonization of *Cutibacterium acnes* (*C. acnes*), and 4) inflammation.[1] Inflammation that occurs causes oxidative stress process, contributing to a further vicious cycle of AV pathogenesis.

Despite the availability of numerous treatment options, including topical and oral medications, many patients experience inadequate or intolerable side effects.[3] Adjuvant therapy with antioxidant supplementation is believed to counteract the oxidative stress process and subsequently lead to clinical improvement. In this report, we compared the case of four patients who presented with mild AV with two patients treated with a combination of oral antioxidants (*i.e.*, zinc and α-lipoic acid) and topical retinoic acid versus two patients treated with retinoic acid monotherapy.

CASES

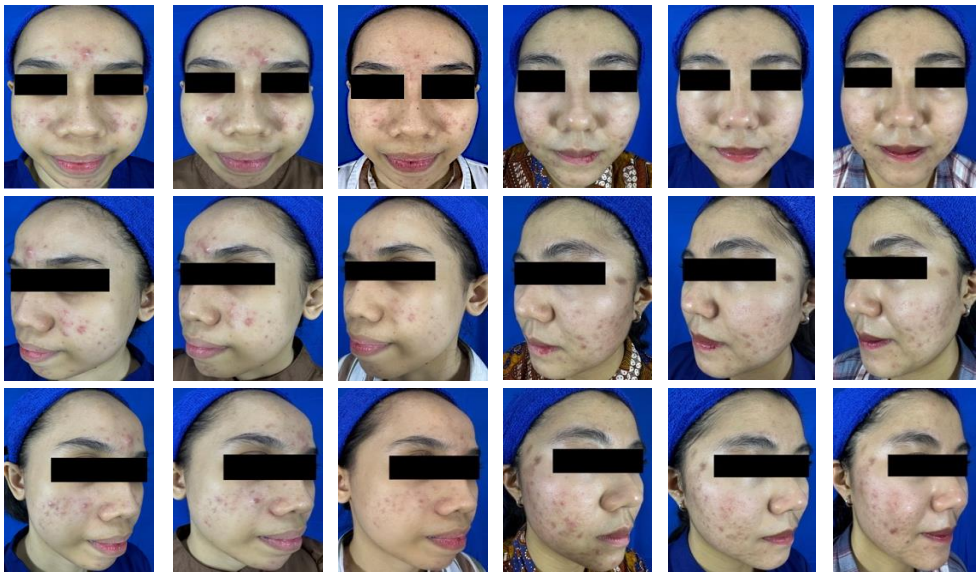
Three 23 yo female patients and one 22 yo female patient presented to the Department of Dermatology and Venereology outpatient with a history of worsening AV of varying duration from 1 to 6 mo. The lesion initially started as flesh-colored papules on the face and progressed into erythematous papules coupled with pustules and spread to the jaw and chin. Complaints of occasional itch and tenderness were reported. Past history revealed a history of AV since puberty varying from 12 to 13 yr. History of medication, atopy, or allergy was denied. Menstruation history was within normal limits. Family history revealed that both parents suffered from AV during puberty till late adolescence.

On physical examination, general examination and vital signs were within normal limits. Dermatological examination revealed multiple open and closed comedones, flesh-colored and erythematous papules, and pustules with total lesions <30 on the facial region (FIGURE 1-2). The patients were diagnosed with mild AV based on the physical examination and Lehmann criteria.

Two patients (Group A: Case 1 and 2) were initiated with combination therapy of oral antioxidant supplementations (50 mg zinc and 100 mg α-lipoic acid) once daily and 0.025% topical retinoic acid cream once daily at night, and the other two patients (Group B: Case 3 and 4) were initiated with 0.025% topical retinoic acid cream monotherapy once daily at night. The patients were followed up for a month every 2 wk. Group A showed a higher improvement of the total lesions by a total decrease percentage of 47.83% and 26.09%, compared to Group B of 27.27% and 12.50%. No notable adverse events were reported.

Group A
Combination of oral antioxidant and 0.025% topical retinoic acid

	Case 1			Case 2		
=	Day 15	Day 29	Day 1	Day 15	Day 29	

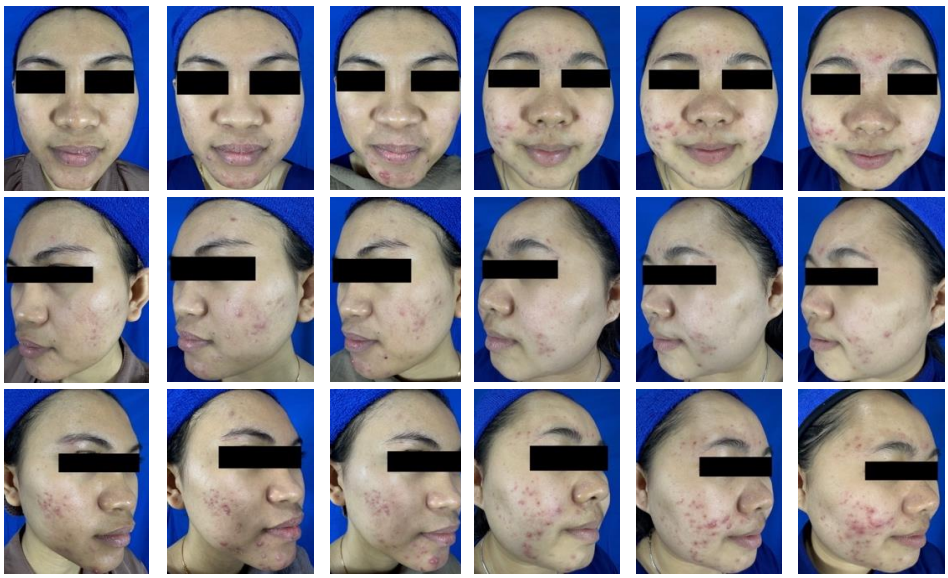


Comedone	11	15	6	14	18	10
Inflammatory lesion	12	6	6	9	4	7
Total lesion	23	21	12	23	22	17

FIGURE 1. Dermatological status of Group A (Case 1 and Case 2) on day 1 and 15 (14 d after treatment), and day 29 (28 d after treatment).

Group B
Monotherapy 0.025% topical retinoic acid

	Case 3			Case 4		
Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	



Comedone	15	12	9	10	7	7
Inflammatory lesion	7	14	7	14	9	14
Total lesion	22	26	16	24	16	21

FIGURE 2. Dermatological status of Group B (Case 3 and Case 4) on day 1 and 15 (14 d after treatment), and day 29 (28 d after treatment)

DISCUSSION

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit and commonly manifests after puberty, with an onset of 12 to 15 yo. The prevalence of AV in adolescents ranged from 26.8-95%, with an estimated prevalence of up to 85%.[1,2] The complexity of AV pathogenesis contributes to the formation of oxidative stress and vice versa. Oxidative stress refers to a phenomenon of imbalance between the levels of oxidants and antioxidants, where excess levels of oxidants are present. Reactive molecules known as oxidants have the capacity to remove electrons from other molecules, cascading an oxidative process.[4,5]

In AV, oxidative stress contributes to the pathobiology of AV via various pathways, including peroxisome proliferator-activated receptors (PPARs), toll-like receptors (TLRs), the mechanistic target of rapamycin (mTOR), and the innate immune system. The PPARs are essential in cellular proliferation and differentiation. In sebocytes, it is believed that PPAR**α** and PPAR**γ** are the critical mediators of lipid metabolism. These receptors are upregulated in AV and can be potently triggered by lipid peroxidation.[6]

Lipid peroxidation is one of the four main classes of oxidative stress process, other than DNA oxidative damage, protein oxidation, and carbohydrate oxidation. This mechanism of lipid peroxidation in AV is supported by an increase of malondialdehyde (MDA; i.e., the most used marker to assess lipid peroxidation), where studies showed a significant gradual increase of plasma MDA based on the AV severity ($p < 0.001$).[4,7,8] The oxidative stress state yield a change in the microenvironment, which cause a conducive micro medium for colonization of the *C. acnes* species and alter the oxygen concentration. In the anaerobic condition and follicles rich in sebum, *C. acnes* will further stimulate pro-inflammatory cytokine release.[4,7]

Toll-like receptors have been suggested to induce the production of pro-inflammatory factors in the human body. It was noted that *C. acnes* lipopolysaccharides might potently provoke TLR2 in monocytes, followed by the secretion of TNF-α, IL-1α, IL-1β, and IL-8, acting as chemoattractants for other immune cells. The IL-8 secreted can profoundly trigger neutrophil chemotaxis, followed by a substantial amount of reactive oxygen species (ROS) by neutrophils, which destroys *C. acnes*. As an off-target of the neutrophil-derived ROS attack, the follicular wall gets degraded and demolished following lipid peroxidation. Subsequently, this process triggers the expression and secretion of more pro-inflammatory factors, such as IL-1α.[6] In terms of mTOR, recent studies demonstrated high levels of mTOR and FoxO1 expression concomitant with increased IGF-1 serum level and deviated FoxO1/ mTROC1 signaling deviation induce AV sebofollicular inflammasomopathy, which is a crucial player in the initiation of oxidative mediated pathways.[6]

The underlying oxidative process rationalizes the use of adjuvant antioxidants. In this report, we focused on oral zinc and alpha-lipoic acid supplementation. Zinc is a crucial trace element for lipid, protein, nucleic acid metabolism, and gene transcription. The exact mechanism of zinc in AV management is yet to be reported. However, it has been postulated to inhibit *C. acnes* proliferation, maintain immunological responses by maintaining macrophage and neutrophil function and chemotaxis, inhibit T helper-17 cell activity, IL-6 and TNF-α production, and downregulating the expression of TLR-2 from keratinocytes. Zinc supplementation aids in decreasing the inflammation process in AV.[9,10] Additionally, zinc deficiency enhances

the conversion of testosterone to dihydrotestosterone, which in turn stimulates sebum production.[11,12] A meta-analysis reported a significant mean decrease of papules compared to placebo in patients treated <12 weeks.[13] These findings support zinc supplementation in AV management.

Alpha-lipoic acid in AV helps to exert its antioxidative and anti-inflammatory effects by decreasing lipid peroxidation and inflammatory markers, i.e., IL-1β, IL-6, IL-8, and TNF-α.[14,15] α-Lipoic acid can be reduced to the dithiol form called dihydrolipoic acid. The oxidized form α-lipoic acid and its active reduced counterpart dihydrolipoic acid, two of the major powerful antioxidants present in nature, have been demonstrated to fight oxidative stress by scavenging a variety of ROS. α-Lipoic acid is able to form a lipophilic complex with Cu^{2+} and protect against Cu^{2+}-induced lipid peroxidation. The α-lipoic acid /dihydrolipoic acid can also maintain cellular antioxidant status by inducing, restoring, and enhancing the synthesis of endogenous antioxidant, e.g., glutathione, vitamin E and vitamin C, subsequently reducing the production of reactive oxygen species.[16,17] α-Lipoic acid increases the expression of γ-glutamyl cysteine ligase, a restriction enzyme in glutathione synthesis, and the cellular absorption of amino acids required for synthesis.[18] Additionally, alpha-lipoic acid has also been reported to aid in hormone regulation, *i.e.*, significantly decreasing testosterone and dehydroepiandrosterone sulphate.[19] Our findings highlighted an earlier and higher clinical improvement in Group A compared to Group B as both subjects in Group A showed a decrease in the number of the total lesions after 14 days of therapy, whereas only one subject in Group B showed a decreased in the number of the total lesions after 14 d of therapy; Case 3 in Group B even showed an increase in the number of the total lesions on day 15 before clinically improved on day 29.

Management of AV is based on the degree of severity and its underlying pathogenesis.[1] Several topical options are available for AV, such as retinoic acid, salicylic acid, and/or benzoyl peroxide, each with varying concentrations. In this case, Group A was initiated with oral antioxidant (zinc and α-lipoic acid) and 0.025% topical retinoic acid cream once daily at night, while Group B was initiated with 0.025% topical retinoic acid cream monotherapy once daily at night. With the finding of an earlier and higher clinical improvement in Group A compared to Group B, it is noteworthy to suggests that oral antioxidants may be a safe and effective adjuvant in managing AV for better therapeutic response in mild AV. Therefore, there are significant knowledge gaps in this area, emphasizing the necessity for additional research on the use of oral antioxidant for AV treatment. This underscores the importance of conducting further studies with a larger number of cases and a developed study protocol to assess the potential benefits and risks associated with oral antioxidant in individuals with AV.

Our cases have several limitations. Firstly, a longer duration of therapy and further follow-up may be necessary. Secondly, a larger number of cases may be required. Lastly, placebo treatment may be evaluated in comparison to oral antioxidant.

CONCLUSION

Acne vulgaris is a multifactorial disorder of the pilosebaceous unit with complex pathogenesis. Comprehensive AV management is based on its pathogenesis and the role of oxidative stress. Adjuvant antioxidant therapy plays a role in reducing inflammation and oxidative stress processes. Earlier and higher clinical improvement was observed in Group A, patients

who received a combination of oral antioxidant and 0.025% topical retinoic acid, indicated by a decrease in the number of total lesions after 14 d of therapy compared to Group B, patients who received 0.025% topical retinoic acid cream monotherapy. Further studies with a larger number of cases and a developed study protocol will be advised.

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