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Effectiveness of oral glutathione in reducing nitric oxide and IL-1α concentrations for clinical improvement in mild to moderate acne vulgaris: a randomized controlled trial

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Abstract

Introduction: Acne vulgaris (AV) is a chronic inflammatory dermatosis predominantly affecting adolescents and young adults. Oxidative and nitrosative stress, marked by elevated nitric oxide (NO) and interleukin (IL)-1α, contributes to AV pathogenesis. Glutathione, a key antioxidant, may attenuate oxidative and nitrosative stress and modulate inflammatory pathways. This study investigates the effectiveness of oral glutathione supplementation on serum NO and IL-1α concentrations, and clinical improvement in mild to moderate AV patients.
Methods: A randomized controlled trial was conducted involving 40 subjects diagnosed with mild to moderate AV. Participants were randomized to receive either 500 mg oral glutathione (n = 22) or placebo (n = 18) once daily for 4 weeks. Clinical severity of AV was assessed utilizing the Lehmann criteria. Serum levels of NO and IL-1α were measured at baseline and week 4.
Results: At week 4, reductions in serum NO and IL-1α concentrations were observed in the glutathione group; however, these changes did not reach statistical significance (p > 0.05). Clinical improvement occurred in seven subjects (31.8%) in the glutathione group, with a reduction from moderate to mild severity. No adverse reactions were reported.
Conclusions: Oral glutathione supplementation demonstrated a non-significant trend toward reducing oxidative and nitrosative stress markers and improving mild to moderate AV. Further studies are recommended to validate these findings.

Keywords: acne vulgaris, oxidative stress, nitric oxide, glutathione, interleukin-1α

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Introduction

Acne vulgaris (AV) is a chronic dermatosis predominantly affecting adolescents and young adults, raising concern and causing patients to seek care and treatment solutions. The exact etiology of AV is yet to be determined. However, the four main pathogenesis factors involved in AV are follicular hyperproliferation, an increase of sebum secretion, inflammation, and colonization of *Cutibacterium acnes* (1, 2).

Oxidative stress is a condition in which the formation of excess reactive oxygen species (ROS) initiates protein, lipid, and nucleic acid damage (3). Several studies have shown an increased concentration of oxidative stress in the skin of AV patients, highlighting its potential burden in the skin and its reflection in the blood (4–6). In addition, nitrosative stress conditions play a crucial role in the pathogenesis of various diseases. An essential component of nitrosative stress is nitric oxide (NO), a major reactive nitrogen species (RNS) constituent. The potential role of NO in pathogenesis is to bind with oxygen anions to become a potent agent of oxidized nitrate, which induces modifications of endogenous nucleic acids and proteins, disrupting oxidative/nitrosative homeostasis (5, 7, 8).

The imbalance triggered by ROS/RNS contributes to the pathobiology in AV through four mechanisms: toll-like receptors (TLRs), peroxisome proliferator-activated receptors (PPARs), the mechanistic target of rapamycin (mTOR) pathway, and the innate immune system. These mechanisms play a role in initiating the increase and release of pro-inflammatory cytokines including interleukin (IL)-1, constituting alpha and beta substypes (8).

Glutathione is known as the "mother of antioxidants" due to its ability to 1) regulate the immune response system, 2) protect and repair cell damage, 3) play a role in toxin, carcinogen, xenobiotic, and detoxification metabolism, 4) repair organs and the skin, and 5) stimulate the production of other antioxidants. As an antioxidant, glutathione is expected to overcome the oxidative and nitrosative stress involved in AV pathogenesis and reduce free radicals as the byproduct of the stress oxidative process (9). This study analyzes the effectiveness of oral glutathione in reducing NO and IL-1α for clinical improvement in mild to moderate AV patients.

Methods

Sample size calculation

A sample size of 18 per group was required to achieve a 95% difference in NO and IL-1α at 4 weeks between groups 1 and 2 for glutathione in mild to moderate AV with 5% alpha and 80% power.

Study design and setting

This was a prospective, double-blind, single-center, randomized controlled trial conducted from November 2020 to April 2021 at a tertiary hospital in Manado, North Sulawesi, Indonesia. The reporting

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of this study adhered to the CONSORT 2010 checklist for reporting randomized trials.

The study was reviewed and approved by the Health Research Ethics Committee of Prof. Dr. R. D. Kandou Manado Hospital (trial registration no.: 068/EC/KEPK-KANDOU/VIII/2020). All participants provided a written informed consent after being briefed in detail about the treatment plan and the expected outcomes, benefits, and risks of treatment.

Research subjects

In this experimental analytical study, a total of 40 subjects were randomly placed into two groups, with 22 subjects in Group 1 (receiving 500 mg oral glutathione) and 18 subjects in Group 2 (receiving a placebo). Consecutive sampling was performed, in which we included any patient with mild to moderate AV that met the inclusion criteria for admission to the dermatology outpatient clinic at Prof. Dr. R. D. Kandou Teaching Hospital.

The inclusion criteria were mild to moderate AV (based on the Lehmann criteria), age 19 to 30, and overall good health. The exclusion criteria included a history of atopy (according to the Hanifin and Rajka criteria), smoking, pregnancy, breastfeeding, use of hormonal contraception, use of AV management (i.e., steroid, topical, and/or systemic antibiotics, and topical and/or systemic antioxidants) within the previous 2 weeks, lifetime consumption of oral isotretinoin, and/or other diseases associated with AV, or underlying systemic disorders that could influence inflammatory or immune responses, such as autoimmune disorders, hematologic abnormalities (e.g., anemia, leukopenia, and thrombocytopenia), or chronic infections. Patients were screened for these criteria through medical history and abnormal full blood count.

Pre-treatment evaluation

A detailed history and clinical evaluation were carried out during the first visit. Baseline data were assessed by calculating the number of non-inflammatory lesions, inflammatory lesions, nodules, and the total lesion count, according to the Lehmann criteria. Pre-treatment clinical photos of the face were taken.

Interventions

Subjects were treated with 500 mg glutathione (Group 1) or a placebo containing saccharine (Group 2). The drug or placebo was taken orally once a day at 9 pm for 4 weeks. Subjects were instructed to keep a record of consuming the drug or placebo and submit their records to the investigators. The drug and placebo were dispensed at baseline and the end of week 2.

Randomization and blinding

All eligible subjects were randomly assigned to two groups, Groups 1 and 2 (Fig. 1), using computerized blocked randomization with a block size of 4. This was done by another consultant in the department that was not associated with the study.

The outer packaging, shape, and dimension of the placebo tablet were made to resemble the glutathione used in Group 1. The investigators and subjects were blinded to the drug given.

Outcomes

The outcomes examined were the core domains for clinical improvement. AV severity was evaluated according to the Lehmann criteria at baseline and week 4. Investigators used digital images of the face taken before treatment to help the assessment.

Secondary outcomes were 1) the concentration of NO and IL-1α at the start of the intervention and at the end of week 4, and 2) adverse reactions during the treatment phase.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM, New York, USA). Data were presented as a number (%) or mean ± *SD* / median (min–max), as appropriate. The analysis included

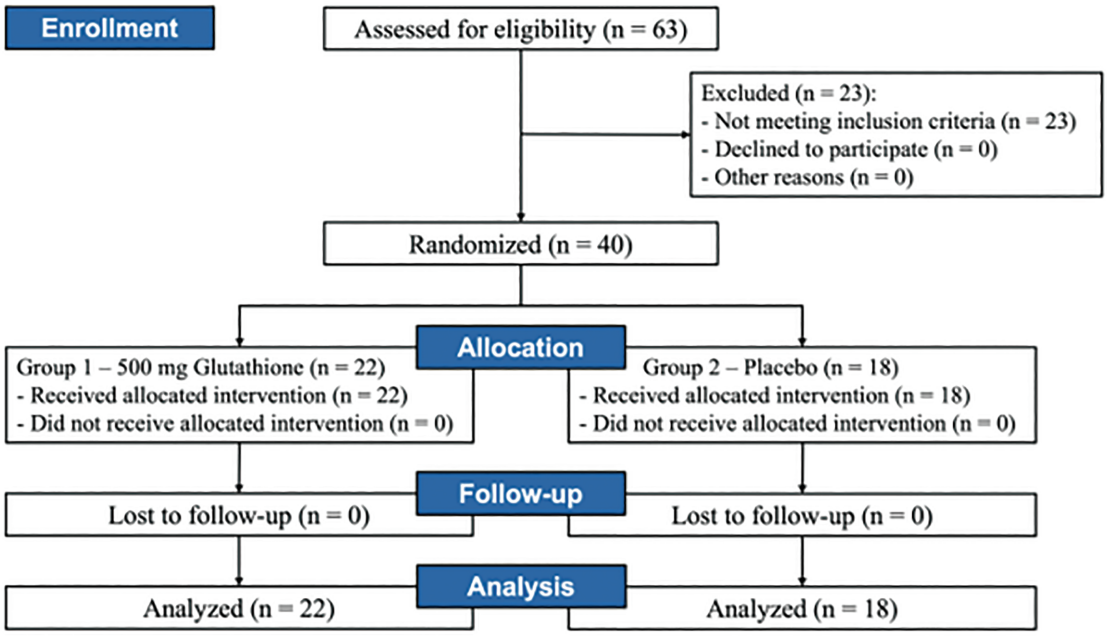

Figure 1 | Study flowchart showing randomization, treatment assignment, follow-up, and analysis.

the Mann–Whitney *U* test to determine significant differences between samples before and after treatment within the same group and between both groups. A *p*-value of < 0.05 was considered statistically significant.

Results

From November 2020 to April 2021, a total of 63 patients were recruited, with 23 subjects not meeting the inclusion criteria. There were no dropouts in the study. A total of 40 patients (14 male and 26 female) were included in the primary and secondary outcome measures (Table 1). There were no reported adverse reactions during the 4-week follow-up.

At baseline, the mean age of patients was 23.50 ± 3.65 years. Group 1 (500 mg glutathione; n = 22) included 12 subjects with mild AV and 10 subjects with moderate AV, and Group 2 (placebo; n = 18) included nine subjects each with mild AV and moderate AV. The medians (min–max) of NO concentration in Group 1 and Group 2 were 12,142 (8,494–42,688) µmol/l and 12,893 (6,248–22,338) µmol/l (p = 0.778), respectively, and the medians for IL-1α concentration in Group 1 and Group 2 were 3,640 (1,320–40,567) pg/ml and 1,962 (1,335–52,305) pg/ml (p = 0.545), respectively.

Response to treatment

The patients were monitored weekly for clinical evaluation and for side effects and complications caused by the drugs. The relation between AV severity and the change in NO and IL-1α concentrations is summarized in Table 2. The relation between the change in AV severity and NO and IL-1α concentrations is summarized in Table 3; in Group 1, seven subjects (31.8%) showed clinical improvement from moderate to mild AV (Figs. 2 and 3).

Table 1 | **Demographics and baseline characteristics of patients.**

Variable	Group 1 (n = 22)	Group 2 (n = 18)	p-value
Sex, *n* (%)			
Male	8 (36.4)	6 (33.3)	0.842
Female	14 (63.6)	12 (66.7)	
Age (yrs)			
Min–max	19–29	19–30	0.499
Mean ± *SD*	23.7 ± 3.9	23.3 ± 3.4	
AV severity			
Mild	12 (54.5)	9 (50.0)	0.775
Moderate	10 (45.5)	9 (50.0)	

SD = standard deviation.

Discussion

AV is a chronic inflammatory dermatological disorder and is currently one of the most common disorders affecting almost all age groups, with the highest incidence among adolescents and young adults. It can be classified into three levels of severity: mild, moderate, and severe. Clinically, it presents with both non-inflamma-

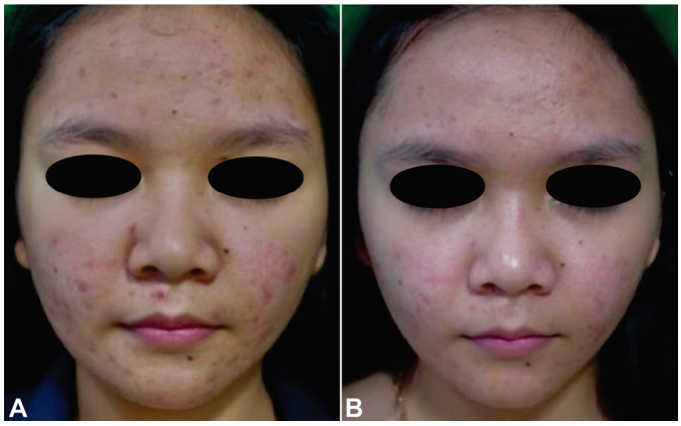

Figure 2 | Acne vulgaris lesions at (A) baseline and (B) the end of week 4 in a subject from Group 1.

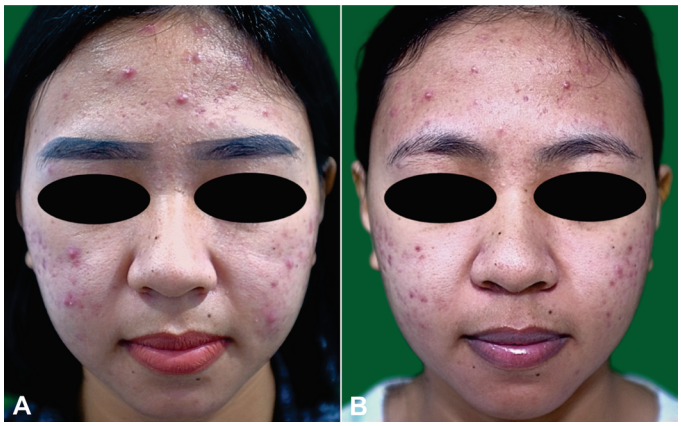

Figure 3 | Acne vulgaris lesions at (A) baseline and (B) the end of week 4 in a subject from Group 2.

Table 2 | **Difference in NO and IL-1α concentrations pre- and post-intervention.**

Concentration	Group 1			Group 2		
	Pre	Post	p-value	Pre	Post	p-value
NO (µmol/l), median (min–max)	12,142 (8,484–42,688)	12,074 (7,771–25,695)	0.661	12,893 (4,248–22,338)	13,357 (5,109–26,145)	0.881
IL-1α (pg/ml), median (min–max)	3,696 (1,320–40,567)	3,757 (1,065–39,051)	0.055	1,962 (1,335–52,305)	1,816 (1,309–60,000)	0.879

IL = interleukin, NO = nitric oxide.

Table 3 | **Difference in NO and IL-1α concentrations pre- and post-intervention.**

		Post-intervention AV severity, *n* (%)		
Concentration	Pre-intervention AV severity	Mild (n = 19)	Moderate (n = 3)	p-value
NO				
Decrease	Mild	6 (100.0)	0 (0.0)	0.031
	Moderate	7 (77.8)	2 (22.2)	
Increase/same	Mild	6 (100.0)	0 (0.0)	1.000
	Moderate	0 (0.0)	1 (100.0)	
IL-1α				
Decrease	Mild	6 (100.0)	0 (0.0)	N/A
	Moderate	3 (100.0)	0 (0.0)	
Increase/same	Mild	7 (100.0)	0 (0.0)	0.250
	Moderate	3 (50.0)	3 (50.0)	

AV = acne vulgaris, IL = interleukin, N/A = not applicable, NO = nitric oxide.

tory and inflammatory lesions, which may progress to acne scar formation (1).

Multiple factors contribute to the development of AV, including genetic predisposition, hormonal influences, environmental exposures, psychological stress, medications, cosmetics, and diet. These factors initiate or exacerbate the pathogenic processes of AV, ultimately leading to clinical manifestations that can affect various body sites, with a predilection for the face, chest, back, and upper arms (1, 10).

Oxidative stress has been a central focus of AV research over the past decades. Evidence indicates that it is not only a consequence of AV progression but also a triggering factor in the development of early inflammatory lesions. The accumulation of oxidative stress, reflected by elevated cutaneous and systemic biomarkers, suggests that its effects may be mitigated through the use of topical or systemic antioxidants (11).

Antioxidants, especially glutathione, may aid in minimizing oxidative stress in AV, as well as nitrosative stress, in which NO plays the leading role (12). NO may play a decisive role in AV pathogenesis. The skin's cell population comprises keratinocytes, endothelial cells, fibroblasts, and various resident or circulating immune cell types. Nearly all of them express isoforms of nitric oxide synthase (NOS), facilitating NO production, which is essential for physiological processes, such as antimicrobial defense, regulation of circulation, and erythematic response to ultraviolet light exposure. Endothelial NOS produces lower levels of NO and inducible NOS produces larger amounts of NO when stimulated by bacterial products or cytokines (13).

NO reacts with reduced glutathione to form *S*-nitrosoglutathione (GSNO); NO will readily react with the sulfhydryl group (-SH) of protein cysteine residues to form *S*-nitrosocysteine, which consists of a redox-mediated posttranslational modification. *S*-nitrosylation is a reversible process that may affect the structure or function of the target cysteine. Therefore, it can be considered a way through which redox-mediated cellular signal is transduced, as well as an endogenous reservoir for NO endocrine functions (12). Through this process, it is believed that oral glutathione consumption helps lower NO concentration, thereby inhibiting the production of ONOO– and ONOOH oxidants, which induce protein modification and endogenous nucleic acid, which disturb the oxidative/nitrosative homeostasis (14).

In our study, the results obtained were not statistically significant, which may be due to several factors: 1) the NO concentration was obtained from blood in which NO is produced from L-arginine protein, which may be influenced by other systemic factors such as diet; 2) the interaction between NO and glutathione can occur at several levels, but in this study it may not have occurred and yielded no effect on nitrosative stress, and/or 3) the glutathione prescribed did not reach the adequate concentration to reduce the NO concentration (15).

In this study, IL-1α reduction was noted in the experimental group after oral glutathione consumption, although it was not significant. Compared to the control group, the experimental group showed decreased proximity to a significant *p*-value. Glutathione shows promise in combating inflammation in mild and moderate AV, where oxidative stress, specifically lipid peroxidation, occurres in the pilosebaceous unit. This process changes the oxygen tension within the follicle, yielding a micro-aerophilic environment facilitating the colonization and survival of *C. acnes* within the unit (16, 17).

All IL-1 family cytokines are expressed, in some variation, within the skin. IL-1α is constitutively expressed by keratinocytes, but it is retained as intracellular stores (18). Early in AV inflammation, neutrophil recruitment activates macrophages, which regulate the migration and adhesion of inflammatory cells by releasing inflammatory factors, such as IL-1α, IL-1β, IL-6, and tumor necrosis factor (TNF)-α (19, 20). IL-1α accelerates the production of keratin 6 and keratin 16, and filaggrin expression in the follicular keratinocytes, leading to abnormalities in architecture and hyperkeratinization, resulting in the narrowing and obstruction of sebum ducts. The keratinocytes in the damaged epidermis also express IL-1α, stimulating further proliferation of neighboring cells and causing the skin to thicken. This may lead to hyperproliferation of keratinocytes and initiation of the process of AV through comedogenesis (21, 22). This is further supported by a study conducted among patients of Greek descent, revealing that a specific genotype of polymorphism of IL-1α poses a risk of AV (23).

This study had a few limitations. First, other parameters of oxidative stress, especially lipid peroxidation, could be further explored. Second, a larger number of subjects and a longer duration of the study could facilitate comprehensive long-term safety and outcome data. Finally, further studies could be performed at other centers and in other geographical regions to analyze the effectiveness of glutathione across different backgrounds.

Conclusions

In this study, oral glutathione supplementation for 4 weeks demonstrated a potential, although not statistically significant, trend in reducing NO and IL-1α in individuals with mild to moderate AV. The clinical improvement observed in the group receiving glutathione suggests that glutathione may aid AV management. Differences in the beneficial effects between groups may be further explored for a potential therapeutic effect of oral glutathione. Given the absence of adverse reactions and antioxidant properties, glutathione may be considered a supplementary treatment alongside conventional acne therapies.

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