The Antioxidant Effect of N-Acetylcysteine and Its Role in the Treatment of Patients with Acne Vulgaris

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Abstract

Background: Acne vulgaris is one of the most common conditions for which patients seek dermatological care and is a common disorder of the skin that affects individuals of all races and ethnicities. There has been an increasing focus on the extent to which oxidative stress is involved in the pathophysiology of acne. The aim of this study is to investigate the effect of N-acetylcysteine, a well known antioxidant, in the treatment of acne vulgaris.

Patients and Methods: This study was carried out on 28 patients of both sexes with age range of 14-30 years who allocated into two groups:Group 1, treated with N-acetylcysteine orally and topical moisturizing cream once daily at bed time for 8 weeks .Group 2: were treated with placebo once daily orally and the same topical moisturizing cream . In addition to 28 healthy people, with age and sex matched group who serve as control group for baseline comparison. Serum malondialdehyde (MDA) and glutathione (GSH) were estimated at baseline and at the end of study after 8 weeks, In addition to clinical follow up.

Results: Administration of N-acetylcysteine to patients with acne vulgaris (Group 1), significantly reduce serum MDA level; and increased serum level of GSH after 8 weeks compared to pre-treatment value, also reduce the number of inflammatory lesions by 21.41% and 48.91% after 4weeks and 8 weeks respectively, compared to placebo.

Conclusion: The results obtained in this study clearly showed the beneficial effect of using N-acetylcysteine to patients with acne vulgaris and confirmed the role of new strategy in the targeting of pathophysiological changes accompanied with acne by using antioxidant agents.

Key words: Acne vulgaris, N-acetylcysteine , antioxidants, oxidative stress.

الخلاصة

الخلفية: حبّ الشباب الشائع أحد الامراض الأكثر شيوعاً للتي تتطلب عناية جلدية وهو مرض جلدي معروف يتعرض له أفرادِ كُلّ الأجناس والإنتماءات العرقية. لقد كَانَ هناك تركيز متزايدُ على المدى الذي يتدخل فيه الإجهادِ التأكسدي في المنشأ المرضي لحبِّ الشباب. إنّ هدفَ هذه الدراسةِ أَنْ تَتحرّى تأثير إن-أستيلسيستين ؛مانع التأكسد المعروف جيدا، في معالجةِ حبِّ الشباب الشائع.

المرضى والطريقة: هذه الدراسةِ نُقِلتْ على 28 مِنْ مرضى كلا الجنسين بمدى عُمرِ 14-30 سنة والذين صنفوا إلى مجموعتين:

مجموعة 1: عولجوا باستخدام إن –أستيلسيستين فمويا وقشطة (كريم) تَرطيب موضعيةِ مرّة يومياً في وقتِ النومِ لثمانية أسابيع . مجموعة 2: عولجَوا باستخدام علاج مموّهِ فمويا ونفس القشطةِ المرطّبةِ الموضعيةِ..هذا بالأضافة إلى 28 شخصَ اصحّاء، مماثلين لخصائص هؤلاء المرضى من حيث العُمرِ والجنسِ يَمثلون كمجموعة قياسيةِ لغرض المقارنة الاولية. تم قياس القيمة الابتدائية لمستوى مادة مالونداياًلديهايد و مادة كلوتاثايون في الدم وكذلك تم قياسهما بعد 8 أسابيعِ من العلاج ، بالأضافة إلى المتابعة السريرية.

النَتائج: استخدام إن_أستيلسيستين إلى المرضى المصابين بحبِّ الشباب الشائع (مجموعة 1)، يُخفّضُ مستوىَ مادة مالونداياًلديهايد في الدم بشكل ملحوظ؛ ويرفع مستوى كلوتاثايون في الدم بشكل ملحوظ بعد 8 أسابيعِ مقَارنةً إلى قيمهما

الابتدائية.. ويخفض عدد الحبيبات الالتهابية بنسب قدرها 38.97% و48.91% بعد ستة أسابيع وثمانية اسابيع على التوالي مقارنة الى العلاج المموه.

الخاتمة: النتائج التي تم الحَصولْ عليها في هذه الدراسةِ أظهرت وبشكل واضح التأثيرَ المفيدَ مِنْ إستعمال إن_أستيلسيستين إلى المرضى المصابين بحبِّ الشباب الشائعِ والمؤكِّدِ للإستراتيجيةِ الجديدةِ في إستهداف تغييراتِ المنشأ المرضي لحبِّ الشباب بإستعمال أدوية مانعِة للتأكسد.

Introduction

Acne vulgaris is one of the most common conditions for which patients seek dermatological care and is a common disorder of the skin that affects individuals of all races and ethnicities. The prevalence of acne in patients with light skin and darker skin appears to be similar (1).Acne vulgaris affects nearly all adolescents and adults in their lives. Although overall health is not impaired, acne is not a trivial disease; it can produce cutaneous and emotional scars that last a lifetime. Numerous psychological problems stem from acne, even resulting in decreased employability in adulthood. Fortunately, acne is eminently treatable (2).Acne has a complex aetiology, involving abnormal keratinisation, hormonal function, bacterial growth, and immune hypersensitivity. The disease is limited to pilosebaceous follicles of the head and upper trunk because the sebaceous glands in these regions are particularly active. The primary acne lesion is the "blackhead" (microcomedo), an impaction and distension of the follicle with improperly desquamated keratinocytes and sebum. The stimulus for comedogenesis is uncertain (3).At puberty, when androgens stimulate the production of sebum, pre-existing comedones become filled with lipid and may enlarge to become visible. Subsequently, some patients also begin to show signs of inflammation. Comedones that become inflamed are nearly always clinically invisible before the pimple develops (4).Inflammatory acne is the result of the host response to the follicular inhabitant *Propionibacterium acnes*, which is a member of the normal flora, largely incapable of tissue invasion or serious infection. The organism metabolises sebaceous triglycerides, consuming the glycerol fraction and discarding free fatty acids. As a consequence of growth and metabolism, *P acnes* produce neutrophil chemoattractants. *P acnes* also activates complement and is generally inflammatory when brought into contact with the immune system (5).In recent years there has been an increasing focus on the extent to which oxidative stress is involved in the pathophysiology of acne. Emerging studies have shown that patients with acne are under increased cutaneous and systemic oxidative stress (6).Recently there has been renewed interest in the influence of oxidative stress and the operations of the antioxidant defense system in acne. Many of these investigations have examined the extent to which a potential oxidative stress burden in the skin might be reflected in the blood of acne patients (7).N-acetylcysteine has an antioxidant action which is believed to originate from its being a precursor of glutathione (GSH), provides the cysteine moiety that is involved in GSH synthesis, so acts as an indirect antioxidant through this way (8). It also possesses a direct free radical scavenging activity against reactive oxygen species (ROS) (9).Based on the above discussions, it would seem reasonable that clinical interventions with oral and topical agents designed to support the antioxidant defense system would be helpful in acne.The aim of this study is to investigate the effect of N-acetylcysteine (NAC), a well known antioxidant, in the treatment of acne vulgaris.

Patients and Methods

A placebo controlled blind study was carried out on 28 patients of both sexes with age range of 14-30 years who attend to outpatient clinic in Al-Hussein Teaching Hospital- Kerbalaa -Iraq over a period

from December 2011 to May 2012, all patients were examined clinically by dermatologist and diagnosed as having acne vulgaris that determined as mild, moderate or severe. Complete history was taken from each patient regarding age, gender, marietal state, duration of the disease, previous treatment and past medical history. Patients were allocated into two groups:

1-Group 1: 14 patients, 7 males and 7 females: were treated with N-acetylcysteine 1200mg/day orally: one effervescent tablet of N-acetylcysteine 600 milligram (Fluimucil; ZAMBON company) twice daily and topical moisturizing cream once daily at bed time for 8 weeks.

2-Group 2: 14 patients, 7 males and 7 females: were treated with placebo capsule (500 milligrams of glucose powder) once daily orally and the same topical moisturizing cream once daily at bed time for 8 weeks.In addition to 28 healthy people, 16 males and 12 females, with age matched group who serve as control group for baseline comparison.From all the subjects 5 ml of blood was collected by vein puncture to estimate the oxidative stress parameters namely malondialdehyde (MDA) (10) and the natural antioxidant Glutathione (GSH) (11); at baseline and at the end of study after 8 weeks. In addition to that, the clinical follow up was done every two weeks in order to assess the changes in the number of inflammatory lesions (12) (the papules and the pustules) and to monitor any side effects that might appear systemically or topically. Statistical analysis: utilizing SPSS software package, student t-test was done, P value ≤ 0.05 considered significant change, all results represented as Mean$\pm$ SD.

Results

As shown in table 1, the baseline mean value for malondialdehyde in patients with acne vulgaris (pre-treatment value) was significantly P ≤ 0.05 higher than that of healthy subjects indicating the existence of oxidative stress in this disease; at the same time, the mean value of serum glutathione "the natural antioxidant "in patients with acne vulgaris was significantly P ≤ 0.05 lower than that of healthy subjects. Results in table 1 showed that administration of N-acetylcysteine to patients with acne vulgaris (Group 1), significantly reduced serum MDA level after 8 weeks by 63.56% compared to pre-treatment value; at the same time serum level of GSH significantly (P ≤ 0.05) increased by 105.55% in group1 after administration of N-acetylcysteine for 8 weeks.In contrast, patients with acne vulgaris who were treated with placebo, show non-significant change in the value of serum level of both MDA and GSH (Group2).

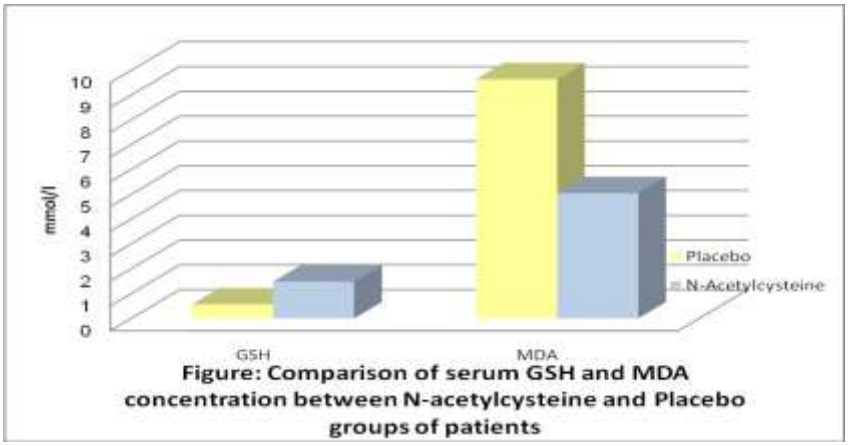

Figure: Comparison of serum GSH and MDA concentration between N-acetylcysteine and Placebo groups of patients

Table 1: pre- and post-treatment values of serum level of malondialdehyde and glutathione of patients with acne vulgaris compared to healthy subjects.

Parameters	Healthy (n=28)	G1 (n=14)		G2 (n=14)	
		Pre	post	pre	post
S. MDA(mcg/ml)	5.46±2.82	8.26±1.24*	5.05±1.75§	9.53±2.21*	9.64±2.21
S. GSH (mcg/ml)	1.61±0.99	0.72±0.25*	1.48±0.68§	0.57±0.25*	0.56±0.29

Results represent mean±SD, G1: N-Acetycysteine, G2: Placebo.
***** represents significant change P≤0.05 compared to healthy subjects.
§ represents significant change P≤0.05 compared to pre-treatment value.

Table 2: Time course changes in the number of inflammatory lesions in patients with acne vulgaris.

Inflammatory lesion no.	G1 (n=14)	G2 (n=14)	P value
Baseline	19.07+6.6	19.29±9.29	0.9445
2 weeks	16.71+5.65	18.71±9.31	0.4981
4 weeks	14.0+4.88	18.0±8.73	0.1465
6 weeks	11.64+4.05*	17.46±8.67	0.0269
8 weeks	9.5+3.59*	17.14±8.78	0.0057

\Results represent mean±SD, G1: N-Acetycysteine, G2: Placebo.
***** represents significant change P≤0.05 compared to pre-treatment value

On the other hand, results in table 2 showed that treatment of patients with N-acetylcysteine reduce the number of inflammatory lesions by 38.97% and 48.91% after 6 weeks and 8 weeks respectively, and this reduction was statistically significant compared to placebo (group 2) that reduce the number of inflammatory lesions only by 12.54% after 8 weeks from starting the treatment.The figure below demonstrates the antioxidant effect of NAC (post-treatment) compared to placebo.

Discussion

Sebum production is considered one of the principal factors involved in acne development. Great efforts have been made and are currently devoted to studying the factors that regulate sebum composition and secretion. In particular, the pathways leading to the formation of lipids typically sebaceous, such as branched fatty acids and fatty acids with uncommon unsaturation patterns, remain to be elucidated. Modifications in the amount, type and, arrangement of fatty acids constituting sebum lipids have been observed in acne patients. By-products of lipid peroxidation, in particular squalene peroxide, have been recognized to play a crucial role in the development of inflammatory reactions as well as in cytotoxicity and comedogenesis (13).It has been shown that lipid peroxidation is one of the important theories of acne. It was postulated that oxidative breakdown of squalene and other skin lipids may not merely be a consequence of the acne process. Rather, lipid peroxides might be directly ‘acnegenic to the skin’. Based on his theory, it was hypothesized that antioxidants would be of value in limiting and preventing the condition via reduction in the formation of peroxides and other oxidation products (14). In the present study the results clearly demonstrated the existence of oxidative stress as a contributory causative factor in patients with acne vulgaris that confirmed the above mentioned evidences. It has been reported that an increase in squalene sets the stage for significantly higher levels of

squalene peroxides and diminished vitamin E in the sebum of acne patients (15). Squalene peroxides also diminish the important skin antioxidant glutathione, while pre-treatment with glutathione depleting agents (DL-buthionine sulfoximine and diethyl maleate) makes the comedogenic potential of squalene peroxides even worse .It has been documented that exposure of peroxidated squalene products to human keratinocyte cells stimulates production of inflammatory cytokines and upregulates lipoxygenase activity (16). Considering that lipoxygenase activity, and leukotriene B4 in particular, has been implicated in promoting inflammation in acne. LTB4 is a chemoattractant well capable of recruiting ROS-generating neutrophils, and its inhibition has been shown to improve acne in clinical research (17).When keratinocytes are exposed to P. acnes surface proteins there is an immediate generation of ROS, most notably superoxide. In addition, the researchers discovered that drugs and nutrients with anti-acne activity - isotretinoin, retinol, zinc sulfate - showed significant inhibition of the P. acnes-stimulated superoxide production. The authors conclude, that inhibition of inflammation 'using appropriate antioxidant molecules could be considered as potential treatment of acne' (18).Additional research seems to confirm that lipid peroxidation is the driving force behind the progression of comedogenesis and inflammation in acne. Examination of comedo samples (20-30 comedones from each patient) removed from acne patients shows that lipid peroxidation is evident even in the earliest microcomedo. As the disease progresses to inflamed lesions there is an up to 4-fold increase in lipid peroxide levels (19). The marked increase in lipid peroxidation once inflammation is ongoing is to be expected. Undoubtedly ROS can provoke the secretion of inflammatory cytokines; however, once initiated, inflammatory chemicals cause a subsequent increase in ROS production (20).Data obtained in this study showed that administration of N-acetylcysteine to patients with acne vulgaris significantly improve the oxidative stress parameters and significantly decrease the number of inflammatory lesions reflecting the beneficial effect of GSH precursor –the N-acetylcysteine – in treating patients with acne vulgaris; a result that can be explained depending on the above mentioned evidences. In conclusion, the results obtained in this study clearly showed the beneficial effect of using N-acetylcysteine to patients with acne vulgaris and confirmed the role of new strategy in the targeting of pathophysiological changes accompanied with acne by using antioxidant agents that may be considered as new and efficient weapon that may be added to the arsenal of combating acne.

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