

Comparison of the Effectiveness of Tretinoin 0.05% Gel and Adapalene 0.1% Gel Based on Clinical Manifestations, and Sebum Levels in Mild Acne Vulgaris Patients

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Abstract: This study aimed to compare the effectiveness of tretinoin 0.05% gel and adapalene 0.1% gel by observing any changes in clinical manifestations and sebum levels before, during and after treatment. This study was carried out in public hospitals and network hospitals in the city of Makassar with double-blind prospective cohort of pre and post treatment. The research sample were thirty-eight patients with mild acne vulgaris who have been observed for the change in the clinical manifestations, measured levels of sebum with sebumeter. The results showed no significant difference between the use of tretinoin 0.05% gel and adapalene 0.1% gel in patients with mild acne vulgaris. There were significant changes of clinical manifestations of two treatment on day 7 and day 14. Levels of sebum by the administration of adapalene 0.1% gel decreased significantly ($p < 0.05$) at day 42, faster than the 0.05% tretinoin gel.

Keywords: Adapalene 0.1% Gel, Clinical Manifestations, Mild Acne Vulgaris, Sebum Levels, Tretinoin 0.05% Gel

1. Introduction

Acne vulgaris (AV) is a chronic inflammatory disease of pilosebaceous follicle characterized by comedones, papules, pustules, nodules and sometimes scars. Blackheads are the early sign of acne lesions, while the papules and pustules are the result of inflammation that gives an overview of erythema and edema which can be enlarged to form nodules. Acne vulgaris were found mainly on the face, neck, upper trunk and upper arms. [1, 2]

The etiology of AV were multifactorial, including genetic, hormonal and bacteria. The cause of acne is still not fully understood. However, there are four main factors that cause the formation of lesions in acne: 1) increased sebum

production by the sebaceous glands, of which androgen has an important role, 2) follicles hyperkeratinization, which causes an enlargement of microcomedone leading to blackheads formation, 3) colonization of the follicle by anaerobic bacteria *Propionibacterium acnes*, and 4) inflammatory reactions. Each inflammation preceded by the hyperkeratinization of follicles. Current therapies target the four factors above to control recurrence and long-term care. [2, 3, 4]

The imbalance between sebum production and secretion capacity will result in hair follicular plugging, where pro-inflammatory cytokine interleukin-1 alpha (IL-1 α) produced by keratinocytes duct promote hypercornification and abnormal differentiation in pilosebaceous units (PSUs) of the infundibulum as seen in the formation of comedones. [5, 6]

Management of AV varies considerably, depend on the type and severity of acne lesions. Topical therapy is indicated for mild (comedonal) to medium AV (papulopustular) without scars. Several factors to consider *in the treatment of acne vulgaris* include the patient's skin color and type as this will affect the formulations choice for topical treatment. Patients with oily skin will benefit from gel or lotion, whilst creams are preferred for those with dry skin. [7, 8]

Topical retinoids alone are the mainstay treatment for comedonal acne, and used in combination with other regimen for moderate to severe acne. Having both comedolytic and direct anti-inflammatory properties, it can be used as maintenance therapy following successful treatment. In addition, it functioned in the normalization of follicular epithelial differentiation and proliferation, thus prevent clogging of pilosebaceous unit, and lower the expression of matrix metalloproteinase (MMP). Introducing of new synthetic topical retinoids or third generation include adapalene and tazarotene, were aimed to compare effectiveness and improve tolerability while still having similar properties to topical tretinoin. [7, 9]

Based on the above reason, we conducted a research to compare the effectiveness of adapalene 0.1% gel to tretinoin 0.05% gel in patients with mild acne vulgaris by observing any alteration in clinical manifestations, and sebum.

2. Subjects

This study used an observational study design with a *double-blind, prospective cohort of pre and post treatment*, conducted at Wahidin Sudirohusodo Hospital Makassar and its hospital network from January to April 2015. Samples were 40 patients with mild acne vulgaris (2 samples were drop out).

3. Procedure

We conducted an interview / direct history taking on acne vulgaris patients who were eligible for research by using questionnaires that had been prepared, followed by clinical examination to establish the diagnose of mild AV. Documentation were performed using a digital camera Nikon Coolpix 20,1 megapixels. Measurements of sebum using sebumeter in patients with mild acne vulgaris were performed at the forehead, nose, chin and cheeks with a focused on T and U area.

4. Result

The study was conducted in Makassar, South Sulawes. Sample consist of 40 people with AV that meet the criteria, who were visiting outpatient clinic of dr. Wahidin Sudirohusodo general hospital and its network hospital. Examinations were performed by observing the clinical manifestations and sebum levels before, during and after treatment. Treatment of AV in this study were adapalene 0.1% gel and tretinoin 0.05% gel for 2 months.

Table 1. Distribution of mild AV patients treated with adapalene 0.1% gel and of tretinoin 0.05% gel based on ages, routine activities and the level of stress Treatment of Acne Vulgaris.

Variables	Adapalene 0.1% gel	tretinoin 0.05% gel	n (%)
	n (%)	n (%)	
Age			
17-25	20 (54.05)	17 (45.95))	37
26-35	0 (0)	3 (100)	3
Routine activities			
Indoor	10 (43)	13 (57)	23
Outdoor	10 (59)	7 (41)	17
Stress level			
Moderate-high	3 (60)	2 (40)	4
Low	17 (49)	18 (51)	35

Note: Chi-square test

Figure 1 shows the comparison of the clinical manifestations with the administration of adapalene 0.1% gel and tretinoin 0.05% gel, showed no significant difference ($p < 0.05$) on days 7, 14, 28, 32 and 56. In this study, the clinical manifestations change by administering adapalene 0.1% gel and tretinoin 0.05% gel, with significant changes ($p < 0.05$) on the 0-7 to 7-14 days and 7-14 days to 14-28.

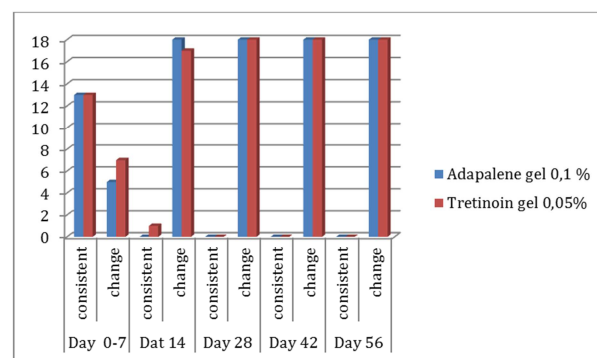


Figure 1. Comparison of clinical manifestations in mild acne vulgaris patients treated with adapalene 0.1% gel and tretinoin 0.05% gel.

Figure 2 shows no significant difference ($p > 0.05$) on the sebum levels after treatment with adapalene 0.1% gel compare to tretinoin 0.05% gel. However, in adapalene group, level of sebum decrease significantly ($p < 0.05$) from day 0 to day 42, whereas in tretinoin group significant reduction occurred on day 56.

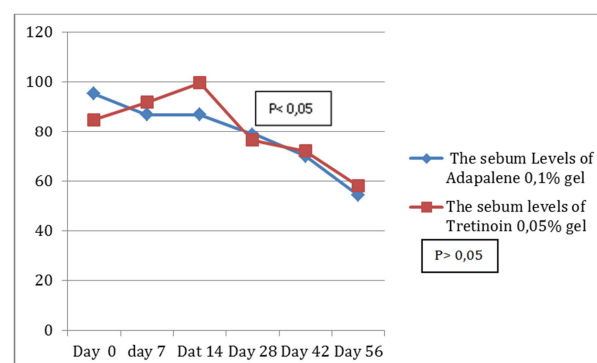


Figure 2. Comparison of sebum levels in patients with mild acne vulgaris treated with adapalene 0.1% gel and tretinoin 0.05% gel.

5. Discussion

Characteristics of the patients evaluated in this study include age distribution, routine activities and the level of stress. Age distribution of AV incidence in this study showed that age 17-25 years were the most prevalent, with the highest number as many as 37 people (92.5%).

Acne vulgaris occurred simultaneously with incidence of adrenarche, which is a period when adrenal glands starts to produce dehydroepiandrosterone sulfate hormones, a precursor of testosterone. [10] Androgens significantly increase the size of the sebaceous gland and stimulates the production of sebum. Furthermore, androgens stimulate keratinocytes proliferation in the sebaceous gland ducts and acroinfundibulum. [11]

This study, the number of AV patients with regular activities in the room were higher than ones who pursued outdoor job, with the amount of 23 people (57.5%). And there was no significant difference regarding routine activities with the use of adapalene 0.1% and tretinoin 0.05%. Also, there were no significant correlation between routine activities with sebum level. The fact that alteration in levels of sebum affected by several factors, not only that activity in the room, especially outdoor activities.

Several factors that may aggravate the degree of AV such as exposure to ultraviolet light, stress, trauma, diet, smoking, and family history are likely to have an influence on the levels of proinflammatory cytokines. Some patients experience their acne lesions increased rapidly after sunlight exposure. [12] Other inflammatory mediators produced by keratinocytes after UVB exposure are nitric oxide and prostaglandins which induce erythema. Furthermore, UVB also induced several other cellular inflammation including mast cell degranulation, TNF- α , up regulation IL-8 and subsequent infiltration of neutrophils in the dermis. [13]

The fact that some patients experience an aggravation of their acne lesion rapidly after exposed to sunlight may be caused in part of the increased vulnerability of their follicles to chemical and physical trauma due to hyperkeratosis. [12]

Acne patients in this study with mild stress levels were as many as 35 people (87.5%). Comparison of stress levels in patients who received treatment of adapalene 0.1% gel and tretinoin 0.05% gel showed no significant difference. Wherein the level of stress in patients with mild AV in this study, are generally exposed to mild stress.

United States National Institutes of Health mentions that stress is one of factor that may induce acne vulgaris. A study of adolescents in Singapore found a significant positive correlation between stress levels and emotional disorders that can lead to exacerbation of acne is unknown. One theory suggest this exacerbation is caused by an increased production of androgen hormones from the adrenal glands and sebum, moreover the level of fatty acids in sebum in also increase. [14]

In this study, mild AV with the administration of adapalene 0.1% gel yielded significant results on days 0-7, days 7-14 and days 14-28. While the administration of

tretinoin 0.05% gel also provide significant improvements. However, differences in changes in clinical manifestations in the administration of adapalene 0.1% gel and tretinoin 0.05% gel obtained is not significant.

Appearances in clinical manifestations on day 42 and day 56, both with treatment adapalene 0.1% gel and tretinoin 0.05% gel, showed no significant changes, Eventhough some patients did improv. This could be due to the fact that clinical manifestations in this study is only in the mild category, as well as the occurrence of many confounded factors such as patients uncontrolled diet, stress, hormonal factors such as menstrual irregularities, which may lead to increase severity of clinical feature.

Additionally, this study showed significant improvement on day 0-7 and day 0-14 on both treatment with adapalene 0.1% gel and tretinoin 0.05% gel. This showed that the use of adapalene gel 0.1% and 0.05% tretinoin gel, at day 7 and day 14 result in improvement of clinical manifestations, which can be caused by the treatment of adapalene 0.1% gel and tretinoin 0.05% gel in patients with mild acne vulgaris. In addition, patients were taking the drug every night for two months of treatment.

Randomized study from various centers with 105 patients with mild to moderate acne vulgaris were treated with adapalene gel 0.1% and tretinoin 0.025% gel for 3 months showed that the efficacy of adapalene was better after 1 week of treatment, with a decrease in inflammatory lesions (32%) and total lesions (28%), however, there were no significant difference after 12 weeks of treatment. [15] Other studies have shown the efficacy of adapalene gel 0.1% compared to 0.1% tretinoin gel, wherein inflammatory lesions decreased after 4 weeks use of 0.1% tretinoin microsphere gel. However, tretinoin group has an irritation effect on the skin. Adapalene 0.1% gel and tretinoin 0.1% microsphere provide almost equal efficacy fter 12 weeks of use. [16]

The imbalance between the production of sebum will lead to its accumulation in the hair follicle and subsequent formation of microcomedones followed by the inflammation process thus becoming inflammatory lesions. [17, 18]

In this study sebum levels decrease significantly on day 48 and day 56 with the treatment of adapalene 0.1%, whereas in 0.05% tretinoin group sebum levels decreased significantly on day 56. However, there is no significant difference in the levels of sebum between the two group after 2 months. This can be caused by chemical characteristics of adapalene which is more stable, less photolabile and more lipophilic, hence allowing it to penetrate into follicle faster than tretinoin.

Adapalene acts by inhibiting the activity of lipooxygenation and oxidative metabolism of arachidonic acid. It is also able to penetrate the stratum corneum and remain in the epidermis and hair follicles, which indeed is the target zone. [19]

In this study, clinical manifestations showed significant improvement on day 14, and significant reduction of sebum level after application of adapalene 0.1% gel and tretinoin 0.05% gel at day 42 and day 56, respectively. These maybe due to the effect of adapalene and tretinoin as retinoid

derivatives on the follicular epithelial proliferation, epidermal proliferation and desquamation causing sebum impelled into infundibulum and comedolysis and stimulate blood vessel to reduce the inflammatory reaction. In addition, retinoids may affect peroxisome proliferator- receptor activated (PPARs), which plays a role in the sebocyte differentiation and maturation that will affect sebum secretion. Thus indirectly, application of adapalene 0,1% gel and tretinoin 0,05% gel may reduce sebum levels.

In addition, sebum secretion is also regulated hormonally. This hormone will still affect the activity of the sebaceous glands until adulthood. In women, a sudden increase in luteinizing hormone following ovulation trigger acceleration of sebaceous glands activity. [5] Approximately 85% of women reported worsening symptoms of AV on premenstrual period [20]. The most common cause of this situation is the change in skin androgen receptor response to physiologic hormonal changes during the menstrual cycle, which related to inflammatory lesions appearance and increased sebogenesis. [21]

From the data above, adapalene 0.1% gel and tretinoin 0.05% gel provide equal effectivity in patients with mild acne vulgaris based on clinical manifestations that provide significant results after 0-7 days and 7-14. However, adapalene 0,1% gel decrease the sebum levels faster than tretinoin 0,05% gel.

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