Comparitive Efficacy of Topical Adapalene Plusoral Azithromycin Versus Topical Adapalene Plus Oral Doxycycline in Treatment of Acne Vulgaris

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ABSTRACT

Objective: To compare the efficacy of topical Adapalene plus oral Azithromycin versus topical Adapalene plus oral Doxycycline in treating mild to moderate acne vulgaris.

Study Design: Quasi-experimental study.

Place and Duration of Study: Dermatology Department, Pak Emirates Military Hospital Rawalpindi, from Jun to Dec 2017.

Methodology: A total of 60 patients were enrolled in the study and were grouped into two groups, A and B, comprising 30 patients in each group. Random tables were used to allocate patients to each group. In this study, Group A was prescribed topical Adapalene be applied as a thin layer over affected areas at night plus oral Azithromycin 250 mg capsule once daily for 03 months, while Group B was given the same instructions for topical Adapalene plus oral Doxycycline100 mg twice daily for 03 months. Fifty percent reduction of lesions from the baseline was considered an effective therapeutic response.

Results: In our patient sample mean age in Group A was 18 years (± 4.77), while the mean age in Group B was 19 years (± 5.12). In Group A, 13 (43%) patients were male, and 17 (57%) patients were female, while in Group B, 12 (40%) patients were male, and 18 (60%) patients were female. Treatment in Group A was effective in 90% of patients, while 73% of patients in Group B showed effective response.

Conclusion: This study concluded that a combination of topical Adapalene plus oral Azithromycin was equally efficacious to topical Adapalene plus oral Doxycycline in treating mild and moderate acne vulgaris.

Keywords: Azithromycin, Acne vulgaris, Doxycycline, Topical adapalene.

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INTRODUCTION

Acne vulgaris is a common dermatological disorder involving blockage or inflammation of pilosebaceous units. It can present as non-inflamed lesions, inflamed lesions, or a mixture of both mostly affects the face, but the back and chest may also be involved.[1]

Pathophysiological factors influencing the development of acne include sebaceous gland hyperplasia,[2] with seborrhea, abnormal desquamation of sebaceous follicle epithelium (comedogenesis), bacterial colonization of the follicle by Propionibacterium acnes and inflammatory and immune reactions.[3]

Inflammatory lesions of acne may be divided into two groups. Less severe cases of acne are associated with pustules and papules and non-inflammatory lesions (comedones). More severe forms are composed of nodules, cysts and even sinuses.[4]

Numerous acne assessment tools have been described, considering various factors, such as type of acne, the severity of acne, number of acne lesions, anatomic location/extent of acne, quality of life and other psychosocial metrics, and scarring among other measures.[5,6]

Adapalene, a naphthoic acid derivative having retinoid receptor agonist properties, has been developed as one of the most effective topical treatments for acne. It modulates keratinization and possesses anti-inflammatory properties. Selective binding of Adapalene to retinoic acid receptors is believed to be due to its lesser capacity to irritate the skin and increased tolerance with greater patient acceptability.[7,8]

Oral antibiotics are helpful in mild to moderate inflammatory acne. Tetracycline group remains the first choice. Macrolides, trimethoprim6and co-trimoxazole 6 are other alternatives for acne.[9]

Azithromycin is a broad-spectrum antibiotic with activity against Gram-positive and some Gram-negative pathogens. The drug stays in tissues for prolonged periods, for 2 to 4 days, at higher levels than the minimum inhibitory concentration for many pathogens.[10]

Our study aimed to validate the comparative efficacy of topical Adapalene,[8] plus oral Azithromycin versus topical Adapalene plus oral Doxycycline in the

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treatment of acne vulgaris to achieve the best results with minimum side effects. In addition, a high level of patient satisfaction. Purpose of the study was to formulate a combination therapy to achieve optimal therapeutic response whilst avoiding antibiotic resistance.

METHODOLOGY

This quasi-experimental study at the Dermatology department of Military Hospital, Rawalpindi, was carried out for six months from June to December 2017. The sample size was calculated using the WHO sample size calculator for two proportions, taking the significance level of 5%, anticipated population proportion P1 was 22.8% and anticipated population proportion P2 was 55.4%.[11]

The calculated sample size was 60. (30 in each group). Non-probability consecutive sampling technique was used.

Inclusion Criteria: Patients of either gender, aged 13 to 24 years, who had mild to moderate acne and did not get any acne treatment in the last three months, were included in the study.

Exclusion Criteria: Patients with cardiac, renal, hepatic disease, or any other concomitant systemic illness, pregnant or nursing mothers, and documented hypersensitivity to Adapalene, Tetracycline, or Azithromycin were excluded. In addition, patients having severe acne i.e. acne conglobata, nodulocystic acne and acne fulminans were not included in the study.

Mild acne was defined as some non-inflammatory lesions, no more than a few papules or pustules but no nodules. In contrast, moderate acne included many non-inflammatory lesions with some inflammatory lesions but no more than one small nodule.[12]

Efficacy is defined as marked improvement seen after some drug is used to treat a condition over a due period of time. Here it was considered positive if there was more than 60% reduction in the acne lesions after 12 weeks of treatment and had to be measured on clinical assessment.[13,14]

Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. Mean and standard deviation were calculated for quantitative variables like age and duration of illness. Gender and efficacy were calculated as frequency and percentages. Efficacy was compared by application of Chi-square test between the two groups. The *p*-value of ≤0.05 was considered significant.

RESULTS

In group-A ages of patients ranged from 12-20 years. Whereas in Group B age range was 21-24 years. In Group A, 13 (43%) patients were male, while 17 (57%) patients were female. In Group B, 12 (40%) patients were male, and 18 (60%) patients were female. In Group A, 16 (53%) patients had a mild severity score 8 of 1-2, and 14 (47%) patients had an average severity score of 3. The mean severity score was 3 with SD ± 2.83. In Group B, 15 (50%) patients had a mild severity score of 1-2, and 15 (50%) patients had a moderate severity score of 3. The mean severity score was 3 with SD ± 2.37 (Table-I).

Table-I: Severity score of the patients.

Severity Score	Group A	Group B
1-2 (mild)	16 (53%)	15 (50%)
3-4 (moderate)	14 (47%)	15 (50%)
Total	30 (100%)	30 (100%)
Mean ± SD	3 ± 2.83	3 ± 2.37

Photographs were taken (after taking patients' consent) before treatment and after 4, 8 and 12 weeks to assess response to treatment and compare both treatment regimes. In addition, patients were asked about abdominal discomfort, diarrhoea, photosensitivity, and other side effects of topical and systemic treatment in each follow-up. Evaluation of number of lesions among two groups showed that Group A 17 (58%) patients had ≤15 lesions while 13 (42%) patients had >15 lesions. The mean number of lesions was 10 with SD ± 3.11. Whereas in Group B, 18 (60%) patients had ≤15 lesions, while 12 (40%) patients had >15 lesions. The mean number of lesions was 11 with SD ± 3.57.

The size of the lesion among the two groups was also registered. 21 (70%) patients of Group A had lesion size ≤0.2cm and 9 (30%) patients with lesion size >0.2cm. The mean size of the lesion was 0.3cm with SD ± 0.12. Whereas in Group B 20 (67%) patients had lesion size ≤0.2cm while 10 (33%) patients had lesion size >0.2cm. The mean size of the lesion was 0.3cm with SD ± 0.10. Cut off limit of the lesion size was kept at 0.2 cm to differentiate between papules and nodules and then classify them into mild or moderate grades (Table-II).

Efficacy among two groups revealed that 27 (90%) patients of Group A showed effective response while 3 (10%) patients did not show marked improvement. At the same time, treatment was effective in 22 (73%) patients of Group B, while 8 (27%) patients did not respond to the treatment (Table-III).

Table-II: Efficacy with respect to severity score.

Severity Score	Efficacy	Group A	Group B	*p*-value
1-2 (Mild)	Effective	15	11	0.1224
	Not effective	1	4	
Total		16	15	
3-4 (Moderate)	Effective	12	11	0.4108
	Not effective	2	4	

Table-III : Efficacy with respect to duration of illness.

Duration	Efficacy	Group A	Group B	*p*-value
≤1 year	Effective	11	8	0.2312
	Not effective	1	3	
Total		12	11	
>1 year	Effective	16	14	0.2378
	Not effective	2	5	

DISCUSSION

Acne vulgaris is one of the commonest inflammatory disorders of the pilosebaceous unit, characterized by papules, pustules, comedones, inflammatory nodules and cysts seen on the face, back, shoulders and chest. Scarring due to acne causes marked psychological distress.[15,16]

In this study, topical Adapalene plus Azithromycin was effective in 90% of patients, while topical Adapalene plus Doxycycline was effective in 73% of patients.

Davis *et al,* have discussed in their study that oral antibiotics should always be used in association with topical retinoids in order to minimize bacterial resistance and for better results.[1] Tetracyclines are the first line indication in patients with moderate to severe acne; Doxycycline and minocycline are most commonly prescribed. Doxycycline at the dose of 100 to 200 mg/day has been shown to reduce the severity and number of inflammatory lesions as per a study by Ghafoor Ullah *et al,* done in Ayub Medical Complex Abbottabad. Efficacy of 22.8% with Azithromycin and 55.4% with Doxycycline group was observed.[17]

Singhi *et al,*[18] had reported that 77% of patients improved in the group receiving Azithromycin compared to 63% in the Doxycycline-treated group, which was statistically significant. However, his study had not used topical Adapalene as done in our study. They had concluded that a combination of topical erythromycin with Azithromycin was significantly better than topical erythromycin and Doxycycline in treating acne vulgaris. In addition, the incidence of side effects was lesser with Azithromycin. This study showed results that were consistent with our study.

Kus *et al,*[19] in their study, reported that acne vulgaris is one of the common inflammatory diseases of the skin. Oral antibiotics are an effective choice in the treatment of this disorder. A randomized, investigator-blinded study was conducted to compare the efficacy of Azithromycin with Doxycycline. One group was randomized to receive a weekly pulse of Azithromycin 500 mg/day for three days in the first month, two consecutive days/week in the next month, and one day per week in the succeeding month. The second group was prescribed Doxycycline 100 mg twice daily for the first month and once daily for two months. Lesions were clinically assessed at baseline and then monthly for three months. Side effects were especially observed. Both drugs showed statistically significant improvement in acne vulgaris. Neither drug was shown to be more effective than the other. Three patients reported diarrhoea in the Azithromycin group, while photosensitivity was observed in two patients on Doxycycline. This study showed that both Azithromycin and Doxycycline are equally effective in treating acne. However, the doses of both the drugs used in this study were different from those we used in our study. Hence the difference in efficacy is seen. Topical therapies may be used as monotherapy, in combination with other topical agents or oral agents in both initial control and maintenance. Topical retinoids are vitamin aderivatives that are prescription agents with randomized, double-blind, placebo-controlled trials supporting their use for acne treatment.

Retinoids are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedone lesion, and are anti-inflammatory. Out of many other options with the advent of newer strategies, topical agents like 5% Dapsone, Clindamycin, Azelaic Acid, and the topical combination of Erythromycin and Tretinoin are showing promising results. Oral therapy includes hormone therapy with spironolactone or combination oral contraceptive pills.[5,11]

Lee *et al,*[20] reported that oral isotretinoin was superior in moderate to severe acne. It has been used in the United States to treat acne for 30 years and is approved by the FDA 10 for the treatment of severe recalcitrant acne vulgaris. Its use has proven successful for most patients with severe acne, resulting in decreased sebum production, acne lesions, and acne scarring, along with a decrease in symptoms of anxiety and depression. It has also been effectively used to treat moderate acne that is either treatment-resistant or that relapses quickly after the discontinuation of oral antibiotic therapy. It is the consensus of the current working group that the presence of moderate acne that is

either treatment-resistant or that produces physical scarring, or significant psychosocial distress is an indication for treatment with oral isotretinoin.[20]

Modern treatments of acne include intralesional steroid 9 injections for large inflammatory lesions. Comedone removal does not affect the course of the disease, but it does improve the patient's appearance.[4] Additionally, some patients may benefit from superficial peels that use Glycolic or Salicylic Acid, although more research needs to be conducted to establish best practices for these modalities. Phototherapy using red or blue light and photodynamic therapy are being assessed as potential treatments for acne.[4] The usefulness of some fractional laser treatments in the management of acne is also being evaluated.[19]

LIMITATIONS OF STUDY

The limitation of the current study was a relatively shorter duration. Depending upon the chronic nature of the disease, large randomized multicentre trials involving follow up at a longer duration are needed to confirm further the results for assessment of the efficacy of different modes of treatment and resultantly reduce the psychological and social burden of one of the most distressing condition may a person face, with an ultimate purpose of improved quality of adult life. In addition, the proper line of therapy should be tailored for every patient according to age and drug tolerability.

CONCLUSION

The study concluded that a combination of topical Adapalene and oral Azithromycin is as efficacious as the combination of topical Adapalene and oral Doxycycline in treating mild to moderate acne vulgaris.

Conflict of Interest: None.

Authors' Contribution

BM: ZIS: SM: Significant.

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