ORIGINAL ARTICLE

THE EFFICACY OF AZITHROMYCIN PLUS LEVAMISOLE VS AZITHROMYCIN ALONE IN THE TREATMENT OF MODERATE TO SEVERE ACNE

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Background: Acne vulgaris (AV) is an inflammatory disorder of pilosebaceous unit and it affects over 85% of teenagers (peak age 17 years) during some point in their lives. Of these 30% have acne severe enough to require medical treatment. The overall incidence is comparable in both genders. Objective was to compare the efficacy of azithromycin plus levamisole with azithromycin alone in the treatment of moderate to severe acne. It was a single centre randomized controlled trial, conducted at the Department of Dermatology at Military Hospital Rawalpindi. **Methods:** We selected 118 patients of acne who fulfilled the inclusion criteria from the dermatology outpatient department. Diagnosis was based on clinical features of acne and severity defined using Acne Global Severity Score. The patients were randomly assigned two treatment groups; Patients in group A received Azithromycin 500 mg per day given for 3 days a week plus oral levamisole 150 mg per day was given for 2 days a week for a total of 08 weeks. Group B patients (n= 59) received Azithromycin 500 mg per day given for 3 days a week for a total of 08 weeks. Patients were followed up fortnightly till they completed their treatment. Response to treatment was graded according to the Acne Global Severity Score. Scoring was done at first visit before therapy and after 08 weeks of therapy in both groups. Therapy was considered efficacious if the patients achieved post-therapy reduction of global score below 19 at the end of 8th week of initiation of therapy. **Results:** Among our 118 study cases, we had 38 male patients while 80 were female patients. The study cases had mean age of 20.10±2.65 years. Mean global severity was 31.25±3.41 while 56 (47.5%) had moderate acne and 62 (52.5%) had severe acne. Efficacy was found to be higher in patients receiving Azithromycin plus levamisole combination. **Conclusion**: Azithromycin plus levamisole was observed as a more effective therapy for the treatment of acne as compared to Azithromycin alone. The study supports the administration of combination therapy for the treatment of Acne to achieve desired outcomes in patients.

Keywords: Acne vulgaris; Azithromycin; Levamisole; Severe acne; Anti-inflammatory role of levamisole; Immunomodulatory antibiotics

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INTRODUCTION

Acne vulgaris (AV) is an inflammatory disorder of pilosebaceous unit and it affects over 85% of teenagers (peak age 17 years) during some point in their lives.[1] Of these 30% have acne severe enough to require medical treatment. The overall incidence is comparable in both genders. [2]

Acne vulgaris is graded as mild, moderate, or severe based on severity of lesions.[3] Mild acne encompasses either non-inflammatory lesions (comedones) or a few inflammatory (papulopustular) lesions, or both. In Moderate form of acne, the lesions are more inflammatory, occasionally nodules, or sometimes both, with mild degree of scarring. Extensive inflammatory lesions and or nodules, with or without scars formation is graded as severe.[3] The development of acne is multifactorial and emanates with the retention of desquamated keratinocytes, leading to inflammation along with *Propionibacterium acnes* residing within the sebaceous follicle; triggering an inflammatory response in macrophages.[4]

Treatment of acne is challenging, and paucity exists in the literature regarding its optimal treatment.[5] Treatment options for acne include topical antibiotics (Clindamycin, Erythromycin, and Tetracycline), topical retinoids, oxidizing agent (Benzoyl peroxide) systemic antibiotics (Doxycycline, Minocycline, Tetracycline, Azithromycin and Erythromycin), systemic retinoid (Isotretinoin) and hormone therapy (combination oral contraceptive pills and spironolactone) depending upon severity of disease.[5] Azithromycin is a macrolide antibiotic which causes RNA dependent arrest of protein synthesis.[6] Azithromycin has multiple leverages when compared to other antibiotics; including lesser gastrointestinal reactions and no major drug interaction. The less frequent dosing regimens improve the patient compliance and acceptability and are also cost-effective.[6]

Levamisole is an anthelminthic agent but also has immune modulatory properties. Through its inhibition of inflammatory cytokines, Levamisole exerts its immune modulatory effect when used as an adjuvant with other drugs such as azithromycin.[7] In one study a combination of Azithromycin plus Levamisole yielded a mean reduction rate for the no. of nodules, cysts, and both of 80.97 % 89.75% and 82.35 % respectively.[8]

Rational of our study was to evaluate efficacy of combining azithromycin and levamisole to target all aspects of acne including inflammatory lesions, comedones, and decrease sebum production.

MATERIAL AND METHODS

This Randomized control trial was carried out at Outpatient Department of Dermatology, Military Hospital Rawalpindi. The study was accomplished over a six-month period from June to December 2017. We used the WHO sample size calculator to calculate the sample size (Confidence level = 95%, Power of test = 90%). The anticipated population proportion (P1) was 82.35 % [8] and population proportion (P2) was 57.99%.[8] The sample size was 118 with random allocation of 59 patients in group A and B. The sampling technique used in the study was non-probability consecutive sampling.

Male and female patients, aged 15–25 years with at least 20 papules or pustules of acne or patients having nodules or cysts due to acne, irrespective of the number of papules or pustules were incorporated in the study. Pregnancy or lactating mothers, patients with history of atopic disorders (Allergy), dermatitis or photosensitivity disorders, patients using any of the systemic treatments for their acne at the time of OPD visit or during the previous month, those with previous history of any haematological, renal or hepatic disease or history of use of alcohol, anti-convulsant or anti-coagulants and those with drug-induced acne were excluded from the study.

The study was conducted after getting approval from the hospital's ethical and research committee. The rationale and benefits of the treatment were made clear to the patients and informed consent in written form was taken. Hospital registration number, name, age, gender, and address with contact phone number was noted for each patient. The disease was diagnosed considering the clinical features of acne and severity was defined using Acne Global Severity Score. Random allocation of patients to treatment was done, those reporting on even dates had fallen in first group and those reporting on odd dates fell in second group. Patients in group A received Azithromycin 500 mg per day given on 3 days a week with levamisole 150 mg per day given on 2 days a week for a total of 08 weeks. Patients in group B received only Azithromycin 500 mg per day given on 3 days every week for 08 weeks. Before start of treatment, careful history & examination, type of lesions was recorded, and patients were kept on follow up fortnightly till the conclusion of treatment.

Response to treatment was graded according to the Acne Global Severity Score. Scoring was done at first visit before therapy and after 08 weeks of therapy in both groups. Therapy was considered efficacious if there was a post-therapy reduction of global score below 19 at the end of 8th week of initiation of therapy.

Complete collected data were entered and analysed in 21.0v SPSS. Quantitative data like age (in years) and severity score was presented as means and standard deviations. Qualitative data like gender and efficacy of the treatment (yes/no) was presented as frequency and percentages. We applied Chi-square test to compare the efficacy between two groups. Effect modifiers like age, gender, residential status, socioeconomic status, disease duration and disease severity were controlled by stratification. After stratification chi-square test was utilized to see their effect on outcome (efficacy). p-value ≤ 0.05 was considered significant.

RESULTS

Our study involved of a total of 118 patients that met the inclusion criteria of our study. Out of these 118 study cases, we had 38 (32.2%) male patients while 80 (67.8 %) were female patients. The study cases had mean age of 20.10±2.65 years (with minimum and maximum age of 15 years and 25 years respectively). Our study outcome has determined that majority among the study cases, i.e., 68 (57.6 %) were aged less than 20 years. Mean acne global severity score in our study was 31.25±3.41 while 56 (47.5%) had moderate acne and 62 (52.5%) had severe acne.

Efficacy was noted in 80 (67.8%) of the study cases where it was noted in 83.1% from patients of group A while efficacy was 52.5% in group B patients (p=0.000).

Distribution of efficacy among study cases

Efficacy	Group A		Group B	
	Frequency	%	Frequency	%
Yes (n=80) 67.8%	49	83.1	31	52.5
No (n=38) 32.2 %	10	16.9	28	47.5
Total	**59**	**100**	**59**	**100**

* $p = 0.001$

DISCUSSION

Ansarin H *et al*[9] studied addition of Levamisole in a double-blind trial. Randomization of 60 patients of acne vulgaris was done into two groups, one receiving doxycycline 100 mg/day with levamisole 2.5 mg/kg/week (up to 150 mg/week) and the other group receiving only daily doxycycline. After 6 months, significant reductions were seen in total lesion counts, the acne severity index and

papule/pustule and nodule/cyst count in the levamisole group.

Another related study done by Rassai S *et al*[8], compared azithromycin alone and azithromycin with levamisole in 169 patients of acne vulgaris.[10] In two months, statistically significant improvements were seen with levamisole with reduced numbers of papules/pustules and nodules/cysts. There have also been numerous reports of the efficacy of levamisole in acne fulminans and acne conglobata.[10,11]

In our study a total of 118 patients met the inclusion criteria. Of these 118 study cases, 38 (32.2%) were male patients while 80 (67.8%) were female patients. A study conducted by Batool et al [12] from Rahim Yar Khan and Ghafoor *et al*[13] from Karak reported 87% and 82% females in their respective studies. Shaukat *et al*[15] from Lahore reported 80 % female gender predominance which is similar to our study. An Indian study conducted by Gupta *et al*[16] reported differently with 63% male gender predominance.

The minimum age of our study cases was 15 years while the maximum age was 25 years with a mean age of 20.10±2.65 years. Mean age of the male patients was noted to be 21.63±2.73 years while that female patient was 19.38±2.29 years. Majority of our study cases (57.6 %) were aged less than 20 years. Batool *et al*[13] and Ghafoor *et al*[14] documented mean age of the acne patients as 18.8±2.7 years and 18.45±2.91 respectively in their study and Shaukat *et al*[14] from Lahore have reported 20.45±3.27 years mean age which is close to our study results. Gupta *et al*[15] from India has reported 22.49±5.38 years mean age.

Mean acne global severity score in our study was 31.25±3.41 while 56 (47.5%) had moderate acne and 62 (52.5%) had severe acne. Hazarika *et al*[16] also had similar results showing severe acne predominating over moderate as demonstrated in our study as well.

Mean duration of illness was 3.52±2.83 months and 60 patients (50.8%) had disease duration of more than 3 months. Batool *et al*[13] documented 55% of patients of less than 3 months duration of illness and Naeem *et al*[17] from Multan have documented similar results.

Efficacy was noted in 80 (67.8%) of our study cases (83.1% in patients of group A while efficacy was 52.5% in group B patients) (p=0.000). A randomized prospective study that included 169 outdoor acne patients divided into 2 groups, to see the effects of Azithromycin plus levamisole (Group A) and Azithromycin alone (Group B) concluded that mean reduction rate for the no. of nodules, cysts, and both in group A were 80.97%, 89.75% and 82.35% while in group B were 58.54 %, 54.55% and 57.99% respectively.[8] These findings are close to our study results. Levamisole appears to be highly effective as a combination therapy with Azithromycin, but further research is required in this regard while using it in routine dermatological practice.

CONCLUSION

A combination of azithromycin and levamisole therapy used in patients of severe acne was found to be more efficacious as compared to azithromycin alone. Our study results support the use of combination therapy for the treatment of moderate to severe acne as it provided better results. Research in additional medicines in acne is need of the hour as acne contributes to majority of patients visiting the dermatology clinic.

Conflict of interest: No conflict of interest to declare by any author.

AUTHORS' CONTRIBUTION

MW, AA, AE: Conceived and design the study. MW, AA: Data collection, data entry, data analysis. MW, AA, AM: Drafted the manuscript. All the authors read and edited the final manuscript.

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