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Original Article

Efficacy of combination therapy with topical fixed dose adapalene 0.1% and benzoyl peroxide 2.5% plus doxycycline 200 mg oral versus oral isotretinoin for the treatment of moderate to severe acne vulgaris

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Abstract

Objective Comparison of efficacy of combination therapy with topical fixed dose adapalene0.1%/ benzoyl peroxide2.5% plus doxycycline 200 mg oral versus oral isotretinoin for the treatment of moderate to severe acne vulgaris.

Methods The study was performed at dermatology section of Lady Reading Hospital Peshawar and a total of 160 patients participated in the study. They were allocated randomly into two groups by lottery method. Those in group A, were given topical fixed dose adapalene0.1%/ benzoyl peroxide2.5% plus oral doxycycline 200 mg and patients in group B received, oral isotretinoin 1 mg/kg/day. Patients were followed up at 12 weeks and response was noted in terms of more than 50% improvement from baseline in total acne burden.

Results In Group A, 45 (56.3%) patients were male, while 35 (43.8%) were female. Similarly, in group B, 50 (62.5%) patients were male and 30 (37.5%) were female. In group A, the total number of lesions decreased from a mean of 76.53 to 23.86 and in group B from mean of 85.05 to a mean of 28.06. The efficacies showed by topical fixed dose adapalene0.1%/ benzoyl peroxide 2.5% plus doxycycline 200 mg and oral isotretinoin are 82.5% and 92.5%, respectively, having no significant difference.

Conclusion Fixed dose preparation of adapalene 0.1%/benzoyl peroxide 2.5% gel in combination with oral doxycycline is equally effective to oral isotretinoin in the management of moderate to severe acne.

Key words
Isotretinoin; Acne vulgaris; Adapalene; Benzoyl peroxide; Doxycycline.

Introduction

Acne vulgaris is a cutaneous disorder that follows a protracted course and predominantly affects the upper torso and face. Typically, they have various presentations ranging from subtle comedones to full blown papulopustular and nodulocystic eruption. More than 85% of the youth suffers from this persistent disorder and have multiple flare-ups throughout adolescent.[1] A portion of hair and its associated structures are affected in this intricate and polygenic condition.[2] The modern comprehension of acne etiology is constantly evolving. Increased sebum production, alteration in the direction of hair

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follicle growth, blockade of the follicular opening, excessive shedding of hair follicle cells and homing with propionibacterium acnes all play an important part in the pathogenesis. Variability in immunity and serotonergic regulatory pathways, along with dietary and genetic factors contribute to additional complexity.[3]

Although not life threatening and often painless, patients often seek acne treatment for aesthetic purposes. The physical symptoms of acne have been associated with psychological co-morbidities including depression, anxiety and low self-esteem, all of which can have a profound effect on quality of life.[4]

The universal approach to treat severe acne is by prescribing isotretinoin orally, but it is associated with a significant adverse events burden and teratogenicity. These risks therefore necessitate frequent clinical and biological monitoring.[5] A significant proportion of the diseased population is reluctant to take the medication due to known adverse reaction profile. Isotretinoin is associated with a number of adverse outcomes including generalized dryness particularly effecting the lips, eyes and nose, a cutaneous rash, gastrointestinal discomfort and inflammation of liver and pancreas. The embryotoxic potential of isotretinoin pose a critical hurdle in its use in procreant age group and require both contraception and supervision.[6]

Owing to these complexities the need for an alternative and equally effective therapy with a higher safety profile is pivotal for the objective management. Both benzoyl peroxide and adapalene are established topical treatments in context of mild acne and there combination provides an enhanced efficacy due to synergism.[7] Their fixed dose combination has both the anti-inflammatory and antibacterial properties. Gold LS *et al*. reported in their findings, that an improvement of fourfold in efficiency was achieved when a combination of topical adapalene and benzyol peroxide was added to oral doxycline 100 mg versus only oral antibiotic in management of moderate to severe Acne.[8]

J. Tan *et al*. also contributed by analyzing the safety and efficiency of a topical combo with oral tretracyclines and isotretinoin while managing cases of acne with extensive involvement. According to their reporting's, the combination group showed an efficacy of 78·2% while isotretinoin showed 92·9%.[9] This blend of topical and oral tetracycline group antibiotics has the potential to replace the oral isotretinoin therapy in those who are not willing or unable to take retinoids. Penna *et al*. also reported in their findings that the addition of topical combination of benzyol peroxide and adapalene to oral antibiotic is a worthwhile alternative to isotretinoin therapy. Their study demonstrated that isotretinoin group had an efficacy of 90% while the combination group promised a success of 72%.[10]

The conducted research will contribute positively to preexisting literature and will provide extra and fresh knowledge regarding the management of moderate to severe acne that will be utilized for further research work.

Methods

Subsequent to acceptance from research and ethical appraisal panel (373/Der/LRH, dated November 22, 2018), all patients who arrived to our Dermatology section, Lady Reading Hospital Peshawar through OPD, diagnosed as acne vulgaris on the basis of evaluation and clinical inspection, fulfilling the inclusion criteria were inducted in the study. The intent of the research was described to the patients. A

well informed agreement and signatures were taken from those who showed interest to participate in the study. Demographic data like age, sex, address, were noted. Patients were allocated randomly into 2 groups, A and B, by lottery method. Group A received doxycycline 100 mg oral twice daily plus topical fixed dose adapalene 0.1%/benzoyl peroxide 2.5% once daily in the evening and group B received oral isotretinoin 1mg/kg once daily. Efficacy was evaluated after 12 weeks of treatment and determined in terms of the percentage of number of lesions cleared from baseline. A clearance of more than 50% of lesions from baseline would be considered effective at 12^{th} week follow up. Telephonic communication would be maintained for compliance. All the detailed information like age, gender and number of lesions were recorded in a specially designed Proforma. By adhering precisely to exclusion criteria the bias and confounders were managed.

The statistical analysis was executed using SPSS 20 version. Averages and standard deviation were determined for continuous variable like age and number of lesions at baseline. Frequencies and percentage was calculated for discrete variables like gender and efficacy. Stratification of efficiency with age, gender and number of lesions was done to understand effect modification. Chi square test was performed to comprehend post stratification in which p value ≤0.05 was regarded as significant.

Results

Total patients that participated in the study were 160. Patients were randomly distributed into 2 groups, A and B, by lottery method. Group A was given Doxycycline 100mg oral twice daily plus topical fixed dose adapalene 0.1%/benzoyl peroxide 2.5% once daily in the evening and group B received oral isotretinoin once daily. 80 patients were included into each group and no patient left the study.

According to gender distribution, 45 (56.3%) male patients were in group A while 35 (43.8%) female patients. Similarly in group B, 50 (62.5%) patients were males and 30 (37.5%) were females. In Group A, the patient's maximum weight was 90 and minimum weight was 41. While in Group B, the patient's maximum weight was 75 and minimum weight was 50. The mean value of weight for group A and group B were, 57.9 and 59.1 respectively. In Group A, the mean value of age of patient was 28.17 and in group B, 31.66 mean value of patients' age was observed. In Group A, the mean value of number of lesions was 76.53 and in group B, 85.05 mean value of no of lesions was observed. In Group A, the mean value of number of lesions was reduced to 23.86 76.53 and in group B, to 28.06 (**Table 1**).

Group A showed an efficacy of 82.5% and Group B showed 92.5%, presented in **Table 2**. Stratification of efficacy with respect to number of lesions is presented in **Table 3**.

Discussion

In our study, result analysis at 12 weeks follow up visit showed that, the treatment regimen of D+A/BPO showed significant decrease in total number of lesions from baseline visit. Isotretinoin showed better response than joint

Table 1 Descriptive statistics of Age, weight, number of lesions

Demographics	*Group A (n=80) Mean±SD*	*Group B (n=80) Mean±SD*
Age (Years)	28.17±10.17	31.66±11.12
Weight (in Kg)	57.9 ± 11.83	59.1±5.67
Number of Lesions before treatment	76.53±27.83	85.05±27.84
Number of lesions at 12 week follow up	23.86±16.5	28.06±16.8

Table 2 Frequency of efficacy.

Efficacy	*Group A*	*Group B*	*P value*
Yes	66 (82.5%)	74 (92.5%)	0.00
No	14 (17.5%)	6 (7.5%)	

Table 3 Stratification of efficacy with respect to number of lesions.

No. of lesions	*Group A efficacy*		*Group B efficacy*		*P-Value*
	Yes	*No*	*Yes*	*No*	
Less than 100	46(57.5%)	10(12.5)	56 (70%)	6 (7.5%)	0.233
Greater than 100	18(22.5%)	6(7.5%)	18(22.5%)	0(100%)	0.979

therapy with oral tetracycline plus topical combination after 12 weeks of management; and the mean of number of lesions at baseline i.e. 85.05 in case of isotretinoin treated group reduced to 28.06 at follow up ,similarly in case of D+A/BPO, it reduced from 76.53 to 23.86 at 12th weeks follow up. In this therapeutic research, treatments with both isotretinoin and Doxycycline group did not produce any such severe adverse effects, warranting the discontinuation of therapy and none of the patients left the trial.

From an efficacy point of view, the combination treatment group is not inferior to isotretinoin with respective efficacies of 92.5% vs. 82.5% a 12th week follow up.

In a study conducted by Tan J *et al.* D+A/BPO showed efficacy in decreasing 80 to 90% of acne lesions in those with severe acne.[9] According to their study isotretinoin performed better then antibiotic plus topical group, and an additional 15% acne burden was reduced from baseline. It is noteworthy, that D+A/BPO group showed a quicker response in decreasing the inflammatory acne at week 2 and week 4. The swift action will benefit those who are not willing for long duration treatment and will also improve the compliance by providing timely results.[9]

Also, an analysis done by Penna P, Meckfessel MH and Preston N shows that the treatment plan of A-BPO/D is more affordable and cheaper as compared to oral isotretinoin in treating severe acne vulgaris.[10]

Tan J *et al.* in their study also reported that, the treatment-related adverse effects with D+A/BPO were far less than isotretinoin. A total of 299 adverse events were seen in 88% of the patients in the isotretinoin arm of their experimental research while 142 treatment-related adverse outcomes were experienced by 53% of the patients in combination therapy arm.[9]

Because of its efficacy and safety in treating severe acne, a regimen of A-BPO/D provides an alternative to oral isotretinoin, especially in patients with medical histories or conditions for which oral isotretinoin is contraindicated.

We have recognized a few shortcomings of this clinical trial. This study didn't take into account the safety perspective. Also our investigative trial was restricted to analyze the comparisons of efficiencies at 12 weeks follow up, whereas the resolution of acne for an extended duration of time is an established advantage of oral isotretinoin.

Results of this investigative research suggest that the combination therapy with D+A/BPO is a worthwhile alternative option in cases of moderate to severe acne.

Conclusion

Conclusion of our study is that the Combination therapy with oral doxycycline 200 mg with fixed dose adapalene 0.1%/benzoyl peroxide 2.5% gel is equally effective as oral isotretinoin in the treatment of moderate to severe acne. This therapeutic combination may give a cost effective substitute for severe acne patients in the management of moderate to severe acne, and may be initiated first in order to treat severe acne in those who are either reluctant to take isotretinoin or intolerant to it.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Author's contribution

HG: Concept, design, data acquisition, drafting of work, final approval and agreement to publication.

JK: Concept, design, data analysis, critical review, drafting of work, final approval and agreement to publication.

MP: Result Analysis, critical review, final approval and agreed to publication.

SMN: Design, result analysis, critical review, final approval of the version to be published.

References

1. Lynn DD, Umari T, Dunnick CA, Dellavalle RP. The epidemiology of acne vulgaris in late adolescence. *Adolesc Health Med Ther*. 2016;**7**:13-25.
2. Williams H, Dellavalle R, Garner S. Acne vulgaris. *The Lancet*. 2012;**379(9813)**:361-72.
3. Zaenglein A, Pathy A, Schlosser B, Alikhan A, Baldwin H, Berson D *et al*. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;**74(5)**:945-73.
4. Nguyen CM, Beroukhim K, Danesh MJ, Babikian A, Koo J, Leon A. The psychosocial impact of acne, vitiligo, and psoriasis: a review. *Clin Cosmet Investig Dermatol*. 2016;**20**;9:383-92.
5. Selya-Hammer C, Boval M, Patel S. adapalene 0.1%/ benzoyl Peroxide 2.5% + Doxycycline 200mg is a less expensive alternative compared to oral isotretinoin for the management of severe nodular acne In Sweden. *Value in Health*. 2015;**18(7)**:A422-23.
6. Choi JS, Koren G, Nulman I. Pregnancy and isotretinoin therapy. *CMAJ*. 2013;**185(5)**:411-3.
7. Sittart J, Costa A, Mulinari-Brenner F, Follador I, Azulay-Abulafia L, Castro L. Multicenter study for efficacy and safety evaluation of a fixed dose combination gel with adapalen 0.1% and benzoyl peroxide 2.5% (Epiduo® for the treatment of acne vulgaris in Brazilian population. *An Bras Dermatol*. 2015;**90(6)**:1-16.
8. Stein Gold S, Cruz A, Eichenfield L. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%–benzoyl peroxide2.5% fixed-dose combination gel with doxycycline hyclate100 mg. *Cutis*. 2010;**85**:94-104.
9. Tan J, Humphrey S, Vender R, Barankin B, Gooderham M, Kerrouche N *et al*. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. *Br J Dermatol*. 2014;**171(6)**:1508-16.
10. Penna P, Meckfessel MH, Preston N. Fixed-dose combination gel of adapalene and benzoyl peroxide plus doxycycline100 mg versus oral isotretinoin for the treatment of severe acne: efficacy and cost analysis. *Am Health Drug Benefits*. 2014;**7(1)**:37-45.