ORIGINAL ARTICLE

EFFECTIVENESS OF ORAL OMEGA 3 IN REDUCING MUCOCUTANEOUS SIDE EFFECTS OF ORAL ISOTRETINOIN IN PATIENTS WITH ACNE VULGARIS

Zarnab Zainab, Naveed Akhtar Malik, Shanza Obaid, Saqib Malik*, Kanza Aftab, Maimoona Mumtaz, Alia Pervez, Zainab Syed***

Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi, *Department of Medicine, Ayub Medical College, Abbottabad, **COMSAT, Islamabad-Pakistan

Background: Acne vulgaris has been a common clinical condition**.** Due to. high prevalence and unclear etio-pathogenesis of acne vulgaris, large number of treatment options have been available across the globe. Limited work has been done to explore the options which may manage or prevent these adverse effects and improve the adherence to the prescribed medications. We therefore conducted this trial to look for effectiveness of oral omega 3 in reducing mucocutaneous side effects of oral isotretinoin in patients with acne vulgaris. **Objective:** To look for effectiveness of oral omega 3 in reducing mucocutaneous side effects of oral isotretinoin in patients with acne vulgaris. It was a randomized control trial conducted at Department of Dermatology Pak Emirates Military Hospital Rawalpindi**.** Ten months, June 2019 to May 2020. **Methods.** A total of 60 patients of acne vulgaris put on oral isotretinoin by consultant dermatologist were included in the study. Patients were randomized into groups by lottery method. Group A received the placebo along with oral isotretinoin while Group B received oral omega 3 in standard dose in addition to oral isotretinoin. Comparison was made in both the groups regarding common mucocutaneous side effects. **Results** Out of 60patients with acne vulgaris and put on isotretinoin included in the study, 26 (43.3%) received placebo in addition to isotretinoin while 34 (56.7%) received omega 3 in addition to isotretinoin. Forty (66.7%) patients were female while 20 (33.3%) were male. Cheilitis 35 (58.3%) was the commonest side effect followed by lip dryness 33 (55%). Application of chi-square test revealed that cheilitis, lip dryness and xerosis were significantly found in more patients who received placebo as compared to those who received omega 3 along with isotretinoin. **Conclusion** Mucocutaneous side effects were a very common finding among patients of acne vulgaris managed with isotretinoin. Cheilitis was the most reported mucocutaneous side effects among the target population. This RCT demonstrated that omega 3 was superior to placebo in order to prevent or manage cheilitis, xerosis or dry lips.

Keywords: Acne vulgaris; Isotretinoin; Mucocutaneous; Omega 3

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INTRODUCTION

Acne vulgaris has been a common clinical condition which usually affects individuals with younger age group of both the genders. It has been prevalent in all parts of the world and general physicians and dermatologist usually encounter these patients on routine basis.[1] People from all the ethnic groups have been sensitive about their skin but facial skin has always been the most sensitive area for the patients especially younger age group. Situation has not been different in our part of the world and facial conditions make the patients really apprehensive and they look for a quick and effective relief.[2]

Due to high prevalence and unclear etio-pathogenesis of acne vulgaris, large number of treatment options have been available across the globe.[3] Multiple local and systemic management options have been in practice for years and many more have been under trials.[4] First phase or early management usually includes topical or mild oral therapies but as the disease advance or scarring occurs then physicians may need aggressive management involving multiple therapies.[5] All the management options may come with their own adverse effects profile as well. Which may need to be managed along with original condtion.[6]

Retinoids have been mainstay of treatment in resistant form of acne vulgaris and despite their efficacy clinicians use them very cautiously because of their adverse effects. Rademaker in 2010 reviewed more than seventeen hundred patients put on retinoids for acne vulgaris for the adverse effects. They came up with the findings that around 78% of the patients suffered from cheilitis during the course of treatment which is a huge number. Eczema was the other common mucocutaneous adverse effect in their study participants.[7] Layton in 2009 published a similar paper highlighting the fact that cheilitis may

be reported by almost 98% of the patients put on isotretinoin. Facial erythema, dermatitis, xerosis and conjunctivitis were the other mucocutaneous symptoms commonly reported by these patients.[8] Mirnizami *et al*. in 2018 did an interesting study regarding the use of oral omega 3 to manage the adverse effects of retinoids. They came up with the conclusion that mucocutaneous adverse effects were significantly less seen among the patients using oral omega 3 along with isotretinoin.[9]Adequate knowledge of these adverse effects and timely recognition and management by the treating dermatologist can help in improving the adherence of the patient towards the prescribed medication and may achieve better therapeutic results.

There has been some work done on adverse effects of isotretinoin among patients of acne vulgaris in our setup. Study of Ahmed *et al*. published in 2005 is important in this perspective. They concluded that mucocutaneous adverse effects have been commonly reported by these patients.[10] Despite availability of adequate data on mucocutaneous adverse effects related with these medications, limited work has been done to explore the options which may manage or prevent these adverse effects and improve the adherence to the prescribed medications. We therefore conducted this trial to look for effectiveness of oral omega 3 in reducing mucocutaneous side effects of oral isotretinoin in patients with acne vulgaris.

MATERIAL AND METHODS

This randomized control trial was conducted at the department of dermatology in Pak Emirates Military Hospital Rawalpindi from June 2019 to May 2020. Sample size was calculated by WHO Sample Size Calculator with population prevalence proportion of 98%,11 margin of error as 5% and confidence level of 95%. Nonprobability Consecutive sampling technique was used to gather the sample for this trial. Patients of both genders with acne vulgaris diagnosed by consultant dermatologist between the age of 18 and 40 and put-on standard dose of oral isotretinoin were included in the study.12,13 Exclusion criteria were the patients with active/recurrent herpes infection or patients with a history of hypertrophic scarring/keloid. Patients with other immunological or systemic conditions with mucocutaneous manifestations were also excluded from the study. Patients with history of allergy or intolerance to oral omega 3 were also excluded from the trial. Patients who could not follow up or refused to become part of the trial were also not included in the study.

Ethical review board committee of the hospital was approached to get the ethical approval for this study. Written informed consent was taken from all the potential participants of this study before the start of study after complete description of the trial and clear understanding of placebo and active treatment. Systemic omega 3 was studied as topical applications to various sites may be cumbersome for a patient and it has limited adverse effects when given orally. It is also cost-effective medication. Moreover, to cover the ethical aspects all participants were given full description and right to leave the study at any time. They were observed closely for any adverse effects.[9] They were told about their right to withdraw themselves at any time from this trial. Patients were divided into two groups A and B. Randomization was done via lottery method, so every patient had equal chances of falling into any of the two groups. Group A received the placebo along with oral isotretinoin (0.5 mg/kg) while Group B received oral omega 3 (1 mg/kg) in addition to oral isotretinoin (0.5 mg/kg).[14] Adverse effects were recorded by an independent dermatologist assessor at the end of three months of treatment in order to ensure that trial remains double blind. Side effects related to dryness were more focused upon in the analysis and they included xerosis, lip dryness, dermatitis, and cheilitis. All these parameters were assessed in detail and diagnosed by consultant dermatologist on basis of objective and subjective findings.[7,9,10]

SPSS 24.0 was used to analyse the data for this study. Mean and standard deviation was calculated for age of the study participants. Frequency and percentages were calculated for gender, various side effects and number of patients which were included in both groups after the process of randomization. Difference in side effects like xerosis, lip dryness, dermatitis, and cheilitis were compared in the both groups with the help of chi-square test keeping *p*-value of less than or equal to 0.05 as significant.

RESULTS

After the application of exclusion and inclusion criteria, informed consent procedure and excluding the patients who were lost to follow up at the end of three months of designated treatment, 60 patients were included in the study. As randomization was not block, rather it was through lottery method so equal number of patients could not be ensured in both the groups. Out of these 60 patients with acne vulgaris and put-on isotretinoin included in the study, 26 (43.3%) received placebo in addition to isotretinoin while 34 (56.7%) received omega 3 in addition to isotretinoin. Table-1 shows characteristics of all the study participants. 40 (66.7%) patients were female

while 20 (33.3%) were male. Cheilitis 35(58.3%) was the commonest side effect followed by lip dryness 33 (55%). Application of chi-square test revealed that cheilitis, lip dryness and xerosis were significantly found in more patients who received placebo as compared to those who received omega 3 along with isotretinoin (p-value<0.05) while dermatitis had no such statistically significant difference among the two groups.

Table-1: Characteristics of study participants (n=60)

Age (years)	
Mean±SD	26.14±6.729 years
Range (min-max)	18–40 years
Gender	
Male	20 (33.3%)
Female	40 (66.7%)
Treatment received	
Placebo	26(43.3%)
Oral omega 3	34 (56.7%)
Common Mucocutaneous side effects	
Cheilitis	35 (58.3%)
Xerosis	31 (51.7%)
Dermatitis	30 (50%)
Lip dryness	33 (55%)
Others	10 (16.7%)

Table-2: Comparison of common mucocutaneous adverse effects between placebo and oral omega 3 group

	Oral omega 3 group	Placebo group	p-value
Cheilitis			
No	23 (67.6%)	02 (7.7%)	<0.01
Yes	11 (32.4)	24 (92.3%)	
Lip dryness			
No	20 (58.8%)	07 (26.9%)	0.013
Yes	14 (41.2%)	19 (73.1%)	
Xerosis			
No	23 (67.6%)	06 (23.1%)	<0.001
Yes	11 (32.4%)	20 (76.9%)	
Dermatitis			
No	16 (47.1%)	14 (53.8%)	0.602
Yes	18 (52.9%)	12 (46.2%)	

DISCUSSION

Acne vulgaris has been one of those skin conditions for which patients have been taking multiple remedies may they belong to alternate medicine group.[3,15]As there may be a lot of theories regarding the disease model for acne vulgaris but no one theory has been fully adopted, therefore a lot of beliefs exist among the masses regarding cause and treatment of this chronic skin condition.[15]Retinoids have been an effective treatment for acne vulgaris and usually used as second line treatment due to multiple mild to severe adverse effects. Despite being teratogenic, they have a lot of other adverse effects as well which may compromise the adherence of treatment by the patients. Mucocutaneous conditions especially those related to dryness of skin and membranes have been found very commonly among the patients using retinoids especially isotretinoin. We therefore planned this study with the rationale to look for effectiveness of oral omega 3 in reducing mucocutaneous side effects of oral isotretinoin in patients with acne vulgaris.

Cannizzaro *et al*. in 2018 conducted a randomized controlled trial to evaluate the efficacy of a cream compound (8% Omega-Ceramides, Hydrophilic Sugars, 5% Niacinamide) which was made to counter the adverse effects of isotretinoin related to mucocutaneous involvement. They concluded that after six months of treatment mixture of 8% omega-ceramides, hydrophilic sugars, 5% niacinamide has been quite effective in reducing the mucocutaneous side effects faced by the patients due to use of isotretinoin.[16] Instead of topic preparation of omega 3 and addition of other compounds, we used oral omega 3 only and compared it with the placebo and it turned out to be effective in reducing cheilitis, xerosis and dry lips in the study participants.

Fabbrocini *et al*. in 2014 evaluated the role of a dietary product which contained gamma linolenic acid, vitamin E, vitamin C, beta-carotene, coenzyme Q10 and Vitis Vitifera in reducing the mucocutaneous adverse effect burden among the patients of acne vulgaris managed with isotretinoin. Their design was quite similar to ours, but they also checked the hydration status and adherence to the therapy. All the side effects related to dryness were less in the group taking this dietary product with better hydration and adherence to the therapy.[17] Similar design in our study highlighted the role of oral omega 3 in reducing mucocutaneous side effects especially related to dryness. This reflects that these supplements should be studied at much higher level and if they have a clear role then guidelines should endorse their use.

Due to positive results of some dietary supplements and vitamins, Kus *et al*. in 2005 performed a trial with vitamin E on these patients but it turned out to be negative and both the arms had no statistically significant difference regarding the side effect profile related to mucocutaneous system.[18]Contrary to the findings of Kus *et al*. our trial was positive and omega 3 oral supplementation proved to be effective. This highlights that some but not all dietary supplements or vitamins may be protective against mucocutaneous adverse effects of isotretinoin.

A recent study done in Iran by Mirnezami *et al*. has been really important in this regard. They did a case control study in this regard and concluded that cheilitis (at weeks 4, 8, and 12), xerosis, dryness of nose at all weeks, and dryness of eyes (at week 4) were less frequent in the group that received

isotretinoin combined with oral omega-3 compared to the group that received isotretinoin alone.[9] Though we did not break the follow up time and reviewed the patients just once after 12 weeks/3 months but our findings were very much similar to them and omega 3 emerged as a protective agent against mucocutaneous adverse effects caused by isotretinoin among patients of acne vulgaris

Multiple limitations make the results of this trial less generalizable. Small sample size was one of the main limitations of this trial. Moreover, patients who dropped out may have become non-compliant or lost to follow up due to adverse effects. Study subjects reporting of adverse effects by the patients may create a bias in the results. Triple, instead of double blinding may as well have increased the reliability and validity of results and made them more generalizable.

CONCLUSION

Mucocutaneous side effects were a very common finding among patients of acne vulgaris managed with isotretinoin. Cheilitis was the most reported mucocutaneous side effects among the target population. This RCT demonstrated that omega 3 was superior to placebo in order to prevent or manage cheilitis, xerosis or dry lips.

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AUTHORS' CONTERIBUTION

ZZ: Paper Writing and Data Collection
NAM: Paper Review
SO: Paper Review and Statistical Analysis
SM: Data Collection
KA: Data Collection
MM: Data Collection
AP: Statistical Analysis
ZS: Data Collection

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Address for Correspondence:

Dr. Zarnab Zainab, Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi-Pakistan
Email: doctorzarnab117@gmail.com