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EFFICACY OF ORAL VITAMIN E IN DECREASING MUCOCUTANEOUS SIDE EFFECT OF ISOTRITINOIN

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ABSTRACT
Isotretinoin represents the treatment that has been shown to induce long-term remissions and even to "cure" acne. A lot of side effects can result from its use especially mucocutaneous, which may lead to discontinuation of the drug. Some reports recommend the addition of vitamin E in oral dose to lower the severity of mucocutaneous side effects of isotretinoin. Study was conducted to investigate the efficacy of oral vitamin E on mucocutaneous side effect of isotretinoin. Forty acne patients receiving isotretinoin 1mg/kg/day were divided in to two groups; with and without 800IU of oral vitamin E and follow up for mucocutaneous side effect over four months duration. In conclusion, this study revealed that despite the administration of vitamin E significantly decrease chelitis which is the most common annoying isotretinoin mucocautonous side effect, additional future studies are needed to confirm our results.

KEYWORDS: isotretinoin, mucocautonous, vitamin E.

INTRODUCTION

The introduction of isotretinoin was a key advance in dermatologic therapy. Isotretinoin is still the only treatment that has been shown to induce long-term remissions and even "cure" acne, because it is the only medication that affects all the etiologic factors implicated in acne: sebum production, comedogenesis, and colonization with *Propionibacterium acnes.* Among natural and synthetic retinoids studied in humans, only isotretinoin has been found to suppress sebum production.

In the early 1980s, using of oral isotretinoin was restricted to patients who suffering from sever nodulocystic acne. However, with increasing experience, its use has been extended to patients with less severe disease who have responded unsatisfactorily to conventional therapies such as topical retinoids plus oral antibiotics. Patients with moderate acne that shows signs of scarring also represent candidates for oral isotretinoin therapy. It was initially considered that optimal benefit would be achieved with an isotretinoin dose of approximately 1mg/kg/day[1]. However, this can induce undesirable dose-dependent effects[2]. Although an effective and generally well-tolerated medication, isotretinoin also has a broad side effect profile. Many of the effects, especially those that are mucocutaneous, are fairly predictable and dose related. Most of the common side effects rarely necessitate the discontinuation of treatment and most spontaneously resolve shortly after cessation of treatment[3]. Mucocutaneous side effects events are by far the most common isotretinoin side effects. A study of two safety trials[4] revealed that the most common adverse mucocutaneous side effects that patients complained about were cheilitis, chapped lips, dry skin, redness or rash, peeling, dermatitis, itching, epistaxis, mucosal dryness, and dry or irritated eyes. These side effects are often dose dependent, and it has been proposed that dividing the dosing into twice daily might decrease them. Cheilitis is almost universal in patients on isotretinoin and it should be considered a treatment failure or an indication of noncompliance if it does not occur. Frequent application of lip balm or petrolatum can provide relief. Dry nasal mucosa and epistaxis occurs in approximately two thirds of patients, and petrolatum may be applied to the nares. Generalized xerosis and pruritus occur in almost half of all patients, most commonly in those prone to atopy before treatment. Patients should be advised to liberally apply emollients and avoid triggers for pruritus and xerosis. Desquamation can occur in some patients but is not common[5]. Many patients will also experience an initial worsening of their acne in the first month. If the patient does experience an initial flare, it will resolve with further treatment. An initial flare of acne can be avoided by starting patients at lower doses of isotretinoin during their first month of treatment. Less commonly, isotretinoin can induce acne fulminans. These cases are rare but, if they occur, treatment should be stopped or the dose decreased and systemic steroids initiated. One report found that a patient with acne fulminans was successfully treated with dapsone without using steroids[6]. Isotretinoin may be restarted at a very low dose after the episode is resolved and increased slowly. Staphylococcal infections are increased in patients on isotretinoin therapy and topical antibiotics may decrease bacterial colonization[7]. There have not been any data on whether the carriage of methicillin-resistant *Staphylococcus aureus* has increased. Less commonly, patients may have stimulation of granulation tissue, leading to pyogenic granuloma eruptions in acne lesions, areas of trauma, and in nail folds. In most cases, these lesions resolve with cessation of therapy, but they may also necessitate the use of oral steroids or silver nitrate if they become fulminant[8,9]. Other types of mucocutaneous effects include diffuse alopecia and increased nail brittleness, most cases completely resolving within two months after ceasing

treatment[5]. Skin atrophy and fragility often occur during treatment and, therefore, the patient should avoid dermabrasion and waxing while taking isotretinoin. Some authors recommend withholding any unnecessary skin procedure (*i.e.*, chemical peels, laser treatments) until 6 months after cessation of treatment to reduce the risk of scarring. The regular use of a lotion with ultraviolet protection should be used to prevent further skin irritation and most mucocutaneous side effects can be improved by the use of dexpanthenol cream, a vitamin B5 analog [10]. There is anecdotal evidence that oral vitamin E (alphatocopherol) can ameliorate the side effects of isotretinoin[11]. Although used commonly with isotretinoin, the current literature is scant and conflicting.

PATIENTS AND METHOD

This study was a randomized case controlled study conducted in Al-Kindy Teaching Hospital through a period of March 2013 to march 2014. Forty patients were enrolled in this study: 24 males and 16 females with mean age of 23.7years. All patients attended out patients' clinic suffering of moderate to severe acne and complete evaluation of their acne and their fitness for isotretinoin oral treatment by clinical examination and full lab investigation regarding complete blood count, lipid profile, blood glucose, level liver and renal function test. The forty patients were divided in to two groups randomly the first one (control) receiving isotretinoin 1mg/kg/day for four months in divided dose which was the treatment period to achieve cumulative dose of 120mg/kg/day and to be followed up monthly for side effects. The second group (case) of twenty patient receiving vitamin E 800IU/day in divided dose in addition to receiving isotretinoin 1mg/kg/day for four months. The patients were screened specially for the following mucocutanous side effects xerosis with pruritus.

TABLE 1: Classification of chelitis according to severity

No chelitis	Mild	Moderate	Severe
0	Dryness only +	Dryness &fissuring ++	Fissuring, bleeding & inability to open mouth. +++

Cheilitis: we divided chelitis according to severity into:
1-mouth, nose (epistaxis), eyes dryness:
2-Skin fragility
3- Retinoid dermatitis
4-Palmoplantar peeling
5-Photosensitivity
6-Sticky sensation (palms, soles)
7-Granulation tissue and pyogenic granuloma-like lesions
8-Nail fragility with softening, onycholysis, paronychia
9-Facial swelling
10-*Staphylococcus aureus* infection
11-Telogen effluvium, hair thinning

Statistical analysis

Statistical analysis was performed using SPSS-21 (Statistical Packages for Social Sciences- version 21) and Microsoft Office Excel (Microsoft Office Excel for windows; 2003). Proportions were compared by chi-square test.

RESULTS

For chelitis 10% of case develops no chelitis, 55% mild, 35% moderate, 0% severe. In regards to control group, 5% develop mild chelitis, 50% moderate and 45% was sever chelitis. P value was 0.001 (table 2) (figure1). The differences between proportions were significant in patients (P 0.0001) and control (P 0.00006). Moreover, the differences between two groups according to severity scores were also significant in mild (P< 0.0005) and sever (P < 0.0006).

TABLE 2: Proportions of chelitis according to severity

Chelitis	No side effect	Mild	Moderate	Sever	Chi square value	P
Case	2(10%)	11(55%)	7(35%)	0(0%)	19.73	0.0001
Control	0(0%)	1(5%)	10(50%)	9(45%)	21.86	0.00006
Chi square value	2.10	11.90	0.92	11.61		
P	0.14	0.0005	0.33	0.0006		

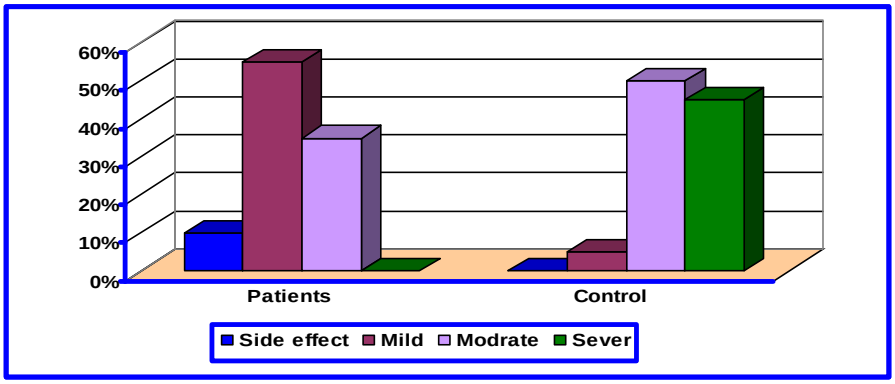

FIGURE 1: Proportions of chelitis according to severity in two groups

Retinoid dermatitis

40% of patients group develop retinoid dermatitis while 45% of control was positive and the difference between two proportions was not significant (P=0.74) (table3)(figure2).

TABLE 3: Proportions of Retinoid dermatitis in two groups

Retenoid dermatitis	Yes	No	Total	p
case	8(40%)	12(60%)	20	0.749
control	9(45%)	11(55%)	20	

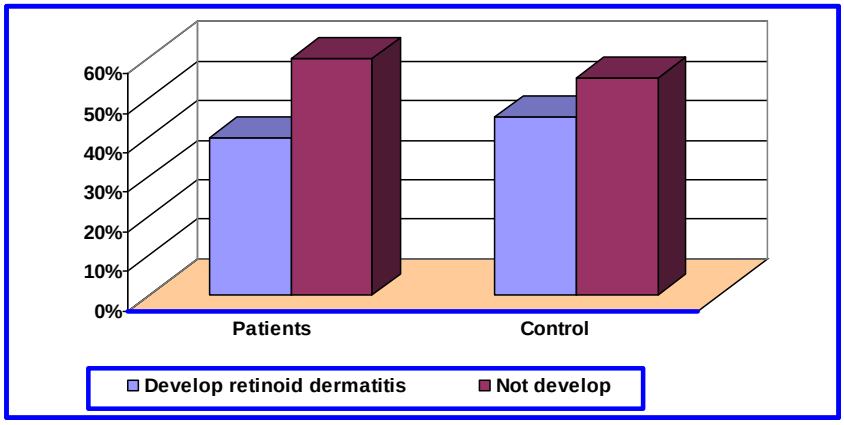

FIGURE 2: Proportions of developed retinoid dermatitis in two groups

Table 4 shows that 30% of patients have skin fragility and the corresponding proportion in control was 55%. The results confirmed that the difference between two proportions was not significant (P =0.109) (table 4) (fig. 3).

TABLE 4: Proportions of skin fragility in two groups

Skin fragility	Yes	No	Total	p
Patients	6(30%)	14(70%)	20	
Control	11(55%)	9(45%)	20	0.109

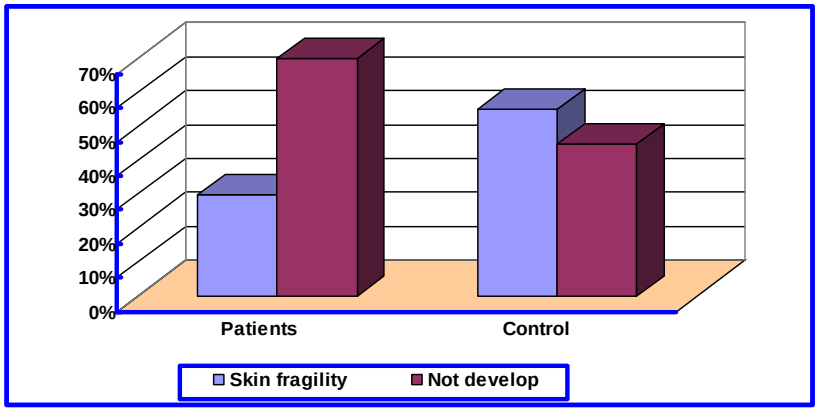

FIGURE 3: Proportions of skin fragility in two groups

Dry mouth mucosa, nose, epistaxis and dry eye

Results revealed that 50% of patients developed a dry mouth while in the control the proportion was 55% (table 5) (figure 4). The difference between two groups in regard with proportions was not significant (P=0.751).

TABLE 5: Dry mouth mucosa, nose, epistaxis and dry eye in two groups

Groups	Yes	No	Total	p
Patients	10(50%)	10(50%)	20	
Control	11(55%)	9(45%)	20	0.751

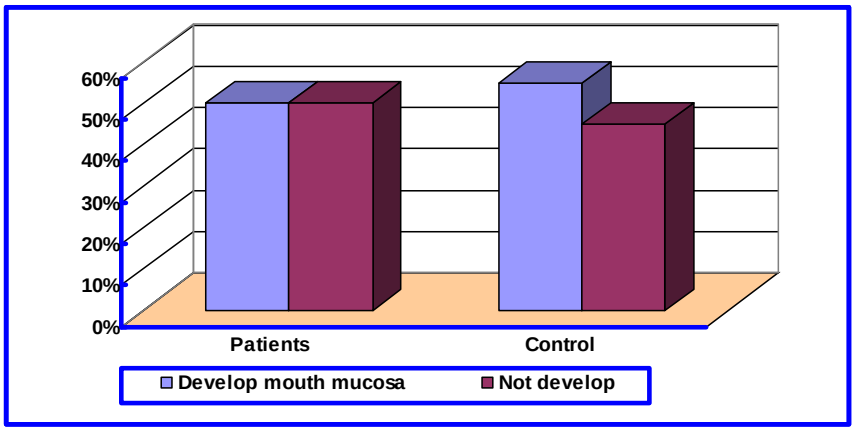

FIGURE 4: Dry mouth mucosa, nose, epistaxis and dry eye in two groups.

Xerosis and pruritis

Statistical analysis shows that the difference between proportions without xerosis and pruritus in patients (60%) and control (40%) was not significant (P=0.201) (table 6) (figure5).

TABLE 6: Proportions with and without xerosis and pruritus in patients and control.

Groups	Yes	No	Total	p
Patients	8(40%)	12(60%)	20	
Control	12(60%)	8(40%)	20	0.201

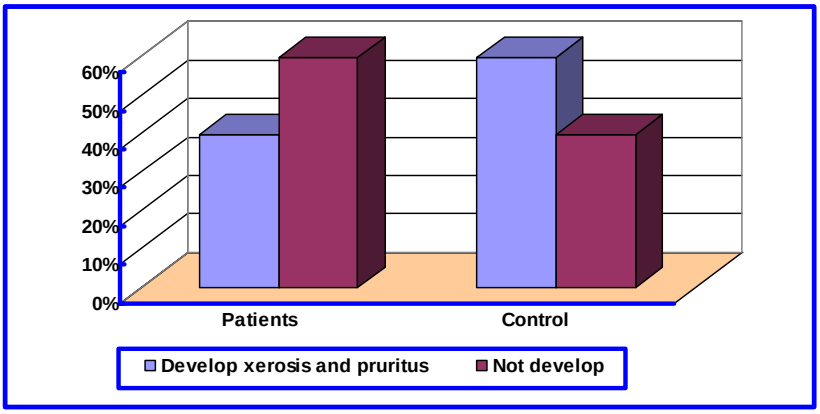

FIGURE 5: Proportions with and without xerosis and pruritus in patients and control.

DISCUSSION

The most common side effect of oral retinoids are mucocutaneous which reflect decreased production of sebum, reduced stratum corneum thickness, and altered skin barrier function. Dry lips or cheilitis is the earliest and the most frequent finding. Dryness of the mouth (accompanied by thirst), nasal mucosa (associated with fragility and epistaxis) and eyes are other potential manifestations. Dry palms and soles and fissuring (particularly of the fingertips) are frequent side effects. Exacerbations of topic dermatitis may occur. Photosensitivity is occasionally observed, in particular with isotretinoin, and probably reflects a reduction in the thickness of the stratum corneum. *Staphylococcus aureus* colonization correlates with isotretinoin-induced reduction in sebum production and may lead to overt cutaneous infections. Diffuse hair loss (telogen effluvium) is a relatively common complaint, although objective alopecia tends to occur only at high dosage levels. Effects on the nail apparatus can include thinning, fragility and shedding of the nail plate as well as paronychia-like changes with periungual granulation tissue. Mucocutaneous side-effect profiles vary among the systemic retinoids. Isotretinoin causes more mucosal dryness[12]. There is some reports advice to add vitamin E to the usual course of oral isotritinoin this may help in decreasing the mucocutaneous side effects which are the most disturbing side effects for acne patients which may lead to discontuation of the treatment. There is anecdotal evidence that oral vitamin E(alphatocopherol) can ameliorate the side effects of isotretinoin[11]. Although used commonly with isotretinoin, the current literature is scant and conflicting. A study was addressing the use of vitamin E in older patients on high-dose (3mg/kg/d). Isotretinoin for the treatment of myelodysplastic syndromes suggests a favorable affect on the mucocutaneous side effects of chelitis, hyperkeratosis, and mucositis[13]. Vitamin E was taken at doses of 800 IU or greater, as compared with the recommended daily allowance of 30 IU. Vitamin E was as effective at 800 IU a day as it was at greater doses. However, a recent double-

blinded, placebo-controlled study with 800 IU a day of vitamin E in patients on lower doses of isotretinoin (1 mg/kg) failed to demonstrate a significant difference in mucocutaneous side effects[14]. Regarding the risks of prescribing vitamin E, are minimal, and toxicity is rare. There are a few patient populations in which vitamin E usage may cause concern. It can prolong the prothrombin time in patients deficient in vitamin K and should not be used in patients that are anticoagulated. A recent meta-analysis suggests increases in mortality and heart failure with the risks of prescribing vitamin E are minimal, and toxicity with chronic disease[15]. In patients older than 55 years of age with a history of vascular disease and diabetes mellitus, there also appears to be an increase in the risk of heart failure[16]. A study of patients with lung cancer suggests that vitamin E increases the cancer risk in those that smoke[17]. Finally, there is evidence that it may decrease the protective effect on HDL of some lipid-lowering agents and cause increases in triglycerides and cholesterol if taken with vitamin C and beta carotene[18]. Overall, if used in the main patient population taking isotretinoin (adolescents and young adults with acne), it is unlikely to cause problems. On the basis of the work of Besa and coworkers, a maximum dose of 800 IU a day is recommended. Interactions between vitamin E and isotretinoin have not been evaluated[13]. Some reports suggest that using retinoids with vitamin E leads to improvements of some side effects due to isotretinoin because vitamin E levels decreased during isotretinoin treatment and some of the side effects due to isotretinoin treatment might be related to this, and supplementation vitamin E may be useful during isotretinoin treatment [19]. Another study from Department of Dermatology, Marmara University School of Medicine, Altunizade, Turkey, concluded that eight hundred IU/day vitamin E did not improve the side-effects of 1 mg/kg/day of isotretinoin in the treatment of acne vulgaris and there was no difference in the incidence and severity of side-effects related[20]. In our study, addition of vitamin E was significantly (P <0.001) reduce chelitis. Regarding to other mucocutaneus side effects, the addition of vitamin E was without advantage. On the other hand there is no reports about side effects from the use of 800IU of vitamin E in our study which are mainly included young adults (mean age was 23.7).

RECOMMENDATIONS

We recommend for further study with larger group sample to screen for more side effects in addition to evaluate the interaction between isotritinoin and vitamin E. As for treatment with isotritinoin in acne patients we advice addition of vitamin E when chelitis started to bother the patients and this will help to continue on treatment.

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