

Efficacy of 3% diclofenac gel for the treatment of actinic keratoses: A randomized, double-blind, placebo controlled study

Iraji Fariba, Asilian Ali*, Siadat Amir Hossein**, Safavai Atefeh, Atar Zadeh Behbahan Seyed Afshin

Departments of Dermatology and *Pharmacology, Isfahan University of Medical Sciences, Isfahan, **Skin diseases and Leishmaniasis Research Center, Isfahan, Iran.

Address for correspondence: Iraji Fariba, Department of Dermatology, Al-zahra Hospital, P.O. Box: 892, Isfahan, Iran.
E-mail: iraji@med.mui.ac.ir

ABSTRACT

Background: Actinic keratoses (AKs) are premalignant skin lesions caused by excessive sun exposure. **Aims:** To explore the therapeutic efficacy of 3% diclofenac in 2.5% hyaluronan gel in the topical treatment of AK. **Methods:** Sixty-four lesions in 20 patients were evaluated. They were randomized to receive either the active treatment, 3% diclofenac in 2.5% hyaluronan gel or placebo, which consisted of the inactive gel vehicle, hyaluronan for a period of three months. The collected data were analyzed by using Student t- tests. **Results:** There was a reduction in the lesion size in 64.7% of diclofenac-treated lesions and 34.3% of control lesions during the three-month course of treatment. Only 9.3% of the lesions in the diclofenac group were completely cleared during three months of treatment. During the treatment, no significant side-effect was observed in both groups. **Conclusion:** Considering the malignant potential of actinic keratoses and the importance of clearing them to prevent their transformation to squamous cell carcinoma, the efficacy of diclofenac gel seen in our study seems to be low. This treatment may be useful for patients who do not tolerate other, more effective kinds of treatment for actinic keratoses.

Key Words: Actinic keratosis, Diclofenac gel, Treatment

INTRODUCTION

Actinic keratoses (AKs) are premalignant skin lesions caused by excessive sun exposure. Although confined to the epidermis, they have the potential to progress to invasive squamous cell carcinoma (SCC)^[1] at an estimated rate of 0.25 to 15% per year.^[2,3] Spontaneous regression in those who reduce their exposure to sunlight or use sunscreens has been reported.^[4] The standard treatment methods for AKs are ablative options, including cryosurgery (the most common method),^[5] surgical excision/curettage and electrodesiccation and dermabrasion. However, a

noninvasive approach is preferable to ablative therapies since topical therapies can reduce the risk of pain, infection and scarring and can treat lesions in cosmetically sensitive or difficult-to-treat locations. These include 5-fluorouracil (5-FU), diclofenac sodium gel 3%, photodynamic therapy (PDT) and imiquimod 5% cream.^[5]

Though Revers *et al*^[6] observed no efficacy with topical diclofenac gel after 30 days, many open-label studies have demonstrated that 3% diclofenac in 2.5% hyaluronan gel is effective in the treatment of AK.^[7-11] The current study was performed to explore further

How to cite this article: Iraji F, Asilian A, Siadat AH, Safavi A, Atarzadeh Behbahan SA. Efficacy of 3% diclofenac gel for the treatment of actinic keratoses: A randomized, double-blind, placebo controlled study. *Indian J Dermatol Venereol Leprol* 2006;72:346-9.
Received: October, 2005. **Accepted:** April, 2006. **Source of Support:** Isfahan University of Medical Sciences, Iran. **Conflict of interest:** None declared.

the therapeutic efficacy of 3% diclofenac in 2.5% hyaluronan gel in the topical treatment of AK.

METHODS

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted between the years 2003 and 2004 in the Isfahan University of Medical Sciences Clinics and Skin Diseases and Leishmaniasis Research Center (SDLRC). The objective was to evaluate the efficacy and tolerability of 3.0% diclofenac in 2.5% hyaluronan gel in comparison with placebo (vehicle gel only) for the treatment of patients with AKs. The drug and placebo were provided by Isfahan Pharmacy School.

Individuals aged 30 years or older, in general good health, with a clinical diagnosis of AKs in at least one of the selected major body areas (forehead, central face, scalp, dorsa of hands) were eligible for inclusion in the study. Informed consent was taken from them. Patients with lesions on the lips were excluded because these lesions had a high risk of transformation to invasive SCC. Women were included only if they were postmenopausal or were using contraception. Patients were excluded if they had a history or were suspected, of hypersensitivity to any of the ingredients of the active or vehicle medication or a history of allergy to aspirin or other nonsteroidal anti-inflammatory drugs. Other exclusion criteria were current treatment with a disallowed medication (e.g., 5-FU, etretinate, cyclosporine, retinoids, topical steroids or recent trichloroacetic acid or glycolic acid peels), unwillingness to discontinue the use of cosmetics or sunscreen on the designated site, treatment with any other investigational drug or participation in another study within the previous 60 days and refusal to undergo a washout period before entry into the study.

Sixty-four lesions of actinic keratosis in 20 patients were evaluated, 32 for active treatment and another 32 lesions with relatively similar characteristics but on the opposite side, as controls. Lesions were randomized to receive either 3% diclofenac in 2.5% hyaluronan gel or placebo (the inactive gel vehicle, hyaluronan only) 0.5 g b.i.d. in each 5 cm²

treatment area for 90 days. All patients were also advised to use a sunscreen and to avoid excessive exposure to the sun. Adverse events were reviewed at each visit from the start of treatment.

The efficacy of the treatment was evaluated using lesion size and the patient's response. Any reduction in the lesion size was considered as a partial response, while complete disappearance of the lesion was considered as complete response. The collected data were analyzed by using Student t- tests and Chi square test with the SPSS program (release 10).

RESULTS

Demographic profile

Sixty-four lesions were evaluated in 20 patients including 27.7% female and 72.3% male patients. Their mean age was 55.1 years old (range, 30-75 years). Lesions were located on the scalp (13%) or on the face (87%).

Efficacy regarding lesion size

In the control group, the mean lesion size was significantly reduced ($p=0.044$) by 8.47% from 0.59 ± 0.56 cm² before treatment to 0.54 ± 0.69 cm² after treatment with hyaluronan gel alone. In the treated group, the mean lesion size was 0.66 ± 0.54 cm² and 0.39 ± 0.44 cm² before and after treatment respectively (40.90% reduction in the mean lesion size), a significant difference ($p < 0.0005$) [Table 1]. The difference between reduction in the mean lesion size was significant between these two groups ($p < 0.0005$).

Efficacy regarding patient's response

In the side treated with hyaluronan gel alone, 34.3% of patients had reduction in their skin lesions, 59.5% had no change, 3.1% (one patient) had worsening and

Table 1: Effect of 2.5% hyaluronan gel alone and 3% diclofenac in 2.5% hyaluronan gel on the mean size of actinic keratosis lesions

Time	Type of treatment	
	2.5% hyaluronan gel	3% diclofenac in 2.5% hyaluronan gel
Before treatment	0.59 ± 0.56 cm ²	0.66 ± 0.54 cm ²
After treatment	0.54 ± 0.69 cm ²	0.39 ± 0.44 cm ²
<i>p</i> value	$p=0.044$	$p= 0.000$

3.1% (one patient) had complete resolution. In the side treated with diclofenac gel, 64.7% of patients had reduction in their skin lesions, 9.3% had complete clearing, 3.1% (one patient) had worsening, while 22.9% had no change.

The Chi square test for patient's response to treatment was significant ($p=0.001$).

Side-effects

Side-effects were limited to negligible. Irritation was seen in eight patients who were treated with diclofenac gel. None of the patients stopped treatment due to side-effects.

DISCUSSION

Our study shows that 3% diclofenac in 2.5% hyaluronan gel provides a somewhat effective but well tolerated treatment for AK. There was a reduction in the lesion size in 64.7% of diclofenac-treated lesions and 34.3% of control-treated lesions during the three months of treatment. However, only 9.3% of diclofenac-treated lesions were completely cured. Our study was the first one that evaluated treated and control lesions in the same patient.

There are a few studies on the efficacy of diclofenac gel in the treatment of actinic keratoses.

In an open-label study that was conducted in 1997 to evaluate the efficacy of topical 3% diclofenac in 2.5% hyaluronic acid for treatment of AKs,^[12] 29 adults were treated for periods ranging from 33 to 176 days (median, 62 days). Of the 29 subjects, 27 were reevaluated 30 days after drug therapy discontinuation. Of the 27 patients, 22 (81%) had a complete response and another 4 (15%) showed marked clinical improvement. The authors concluded that topical 3% diclofenac in 2.5% hyaluronic acid gel might be a clinically useful topical agent for the treatment of actinic keratoses.^[12] In another study, the investigators achieved no significant differences in AK clearance when patients were treated with 3% diclofenac gel for 30 days versus vehicle.^[6]

In another randomized, double-blind, placebo-

controlled trial involving outpatients with a diagnosis of five or more AK lesions contained in one to three 5 cm blocks,^[11] patients received either active treatment (3% diclofenac gel in 2.5% hyaluronan gel) or inactive gel vehicle (hyaluronan) as placebo (0.5 g b.i.d. in each 5 cm treatment area for 90 days). Results obtained from 96 patients at follow-up (30 days after end of treatment) indicated that a significantly higher proportion of patients who received active treatment cleared as compared to the placebo group.^[11]

In another study, the efficacy and tolerability of twice daily diclofenac sodium gel (3.0%) in the treatment of AK for a treatment period of 90 days and a 30-day follow-up period, was evaluated.^[7] At Day 90 of treatment, 78% of patients had $>$ or $=$ 75% AK lesion clearance based on the target lesion number score (TLNS). Improvement was further observed in 85% patients who demonstrated more than or equal to 75% AK lesion clearance at Day 120 (follow-up). Dry skin and rash at the application site were the most commonly reported adverse events and most of these adverse events were mild or moderate in severity.^[7]

The efficacy of diclofenac gel in AK seems to be low in our study. We suggest randomized double-blind study comparing the efficacy of diclofenac gel with that of 5-fluorouracil to determine whether the use of diclofenac gel as a first-line treatment for AK is logical.

We conclude that 3% diclofenac in 2.5% hyaluronan gel is safe, but only somewhat effective for the treatment of actinic keratosis. It may be useful for patients who do not tolerate other, more effective kinds of treatment for actinic keratosis.

REFERENCES

1. Schwartz RA. The actinic keratosis. A perspective and update. *Dermatol Surg* 1997;11:1009-19.
2. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet* 1988;1: 795-7.
3. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment: A patient-oriented perspective. *Arch Dermatol* 1991;127: 1029-31.
4. Marks R, Foley P, Goodman G, Hage BH, Selwood TS.

- Spontaneous remission of solar keratoses: The case for conservative management. *Br J Dermatol* 1986;115:649-55.
5. Jorizzo JL. Current and novel treatment options for actinic keratosis. *J Cutan Med Surg* 2004;8:13-21.
 6. Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin, Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002;146:94-100.
 7. Nelson C, Rigel D, Smith S, Swanson N, Wolf J. Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). *J Drugs Dermatol* 2004;3:401-7.
 8. Rivers JK. Topical 3% diclofenac in 2.5% hyaluronan gel for the treatment of actinic keratoses. *Skin Therapy Lett* 2004;9:1-3.
 9. Tutrone WD, Saini R, Caglar S, Weinberg JM, Crespo J. Topical therapy for actinic keratoses II: Diclofenac, colchicine and retinoids. *Cutis* 2003;71:373-9.
 10. Jarvis B, Figgitt DP. Topical 3% diclofenac in 2.5% hyaluronic acid gel: A review of its use in patients with actinic keratoses. *Am J Clin Dermatol* 2003;4:203-13.
 11. Wolf JE Jr, Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol* 2001;40:709-13.
 12. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997;133:1239-42.