*Original Article*

# Comparison of the efficacy of cryotherapy and 0.1% Acnalen gel vs. cryotherapy and placebo in the treatment of actinic keratoses

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**ABSTRACT**

***Objective:*** To compare efficiency of cryotherapy followed by Acnalen gel 0.1% with cryotherapy plus placebo in the treatment of AKs (Actinic Keratosis).

***Methodology:*** One hundred outpatients who had a clinical diagnosis of actinic keratoses on face or scalp with at least five lesions were enrolled in the study. Patients were randomized into two groups: cryotherapy plus placebo and cryotherapy plus Acnalen 0.1% gel for a period of 100 days. Lesion counts were assessed at baseline, and 40, 70 and 100 days after cryotherapy.

***Results:*** Mean baseline number of lesions for cryotherapy plus Acnalen gel group and cryotherapy plus placebo group were 7.54±3.66 and 7.20 ± 3.60. In Acnalen group mean number of lesions reduced to 3.44±2.71(54.79±3.8%↓) and in placebo group reduced to 3.68±2.97 (48.60±4.5%↓) (P=0.62).

***Conclusions:*** Our results suggested that cryotherapy and Acnalen 0.1% gel during 100 days cannot be more helpful than cryotherapy alone in the treatment of clinical AKs.

**KEY WORDS:** Actinic keratoses, Cryotherapy, Acnalen 0.1% gel.

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## INTRODUCTION

Actinic keratosis are the lesions induced by cumulative effects of UV (Ultraviolet) that may occur in sun-exposed areas of skin[1,2] and have the prevalence of 11-25 percent; these lesions are pre-malignant and have the moderate risk (6-16 percent) of conversion to SCC. Therefore, early diagnosis and treatment of all actinic keratosis lesions is very important.[1,3,4]

Nowadays, two treatment methods are advocated for actinic keratosis lesions that include destructive and topical medication. Destructive methods are limited to the lesion itself (lesion-directed) and have no use in treatment of sub-clinical lesions and skins damaged from sunlight; but the topical pharmacological treatment methods can be used in whole lesion area (field-directed). The advantage of pharmacological approaches is that, in addition to treating clinical lesions, they also improve the sub-clinical and non-visible lesions.[1,3,5] These methods

are non-invasive and often applicable by the patient themselves; their irritation risk, pain, infection and scar are minimal.[1,5,6]

Cryotherapy has been a most common destructive method in treatment of actinic keratosis lesions[2,7] and is simple and low cost.[8-10] Improvement rate of lesions with cryotherapy has been reported between 75-98 percent.[11] In some studies, topical retinoid has been effective in improvement of clinical demonstrations of sunlight-damaged skins including actinic keratosis.[12,13]

Considering the relatively high prevalence of actinic keratosis, importance of its treatment and since Adapalen 0.1% gel is domestically produced (Acnalen™) and is very affordable and no study has yet been conducted evaluating its effect on increasing the effectiveness of cryotherapy. This study was conducted to investigate this issue in order to replace merely destructive cryotherapy treatment with a combined therapy of cryotherapy and Adapalen.

## METHODOLOGY

A randomized, double-blind clinical trial was performed on patients with actinic keratosis on the face or scalp from January 2010 to March 2011 in Sina hospital; the effect of cryotherapy alone, and Acnalen 0.1% gel with cryotherapy and placebo was studies in the treatment of actinic keratosis.

Patients with actinic keratosis were randomly divided into two groups. The two groups under study were matched in terms of age, sex, location and number of injuries. Pregnant people, patients with a history of previous allergy to drugs or methods used, recipients of destructive or medical therapeutic methods for lesions during the past month and isotretinoine in the past two months were excluded.

Acnalen gel (generic name Adaplen) and placebo (as the carrier gel) with the same color and appearance were in similar 30 gram drug tubes; that the patients and the evaluators were both blind to the type of drugs.

At baseline, cryotherapy was performed on all patients once by spraying liquid nitrogen on each lesion for about 10-15 seconds so that a 2mm freezing circle was composed around the lesion. Then, 10 days after cryotherapy (day 10 of study), patients, after the visit and re-examination of the possible complications, were randomly entered one of two treatment groups with a code assigned, and received their drug tubes containing Acnalen or placebo monthly per visit (till the end of treatment, i.e. three months). In each group, drug was used by patients on the total area of the lesion twice a day until the last day of the study (the whole course of medication = 90 days).

Patients in each group were examined by therapeutic dermatologist on days 0, 40, 70 and 100 of study and the number of lesions was recorded. Digital serial photography on patient consent was done at days 0, 70 and 100. Outcome of the treatment was expressed as a change in the number of lesions where:

*Full recovery:* ≥75% reduction in the number of lesions

*Relative recovery:* 30 to 75 percent reduction in the number of lesions

*No Response:* no reduction or ≥30% reduction in the number of lesions

*Worsening:* An increase in the number of lesions.

Complications of treatment in both groups were recorded through clinical examination and also questioning the patients. They included pruritus, dyschromia (hypo or hyperpigmentation at the site of treatment) and scar formation.

Data obtained from the study were statistically analyzed by descriptive-statistical methods (frequency, percentage and mean ± SD), comparison test of the difference between the two mean values and the chi-square test and using SPSS.16 statistical software. Normality of data distribution was evaluated by Kolmogorov - Smirnov test. In this study, significance level was set to 0.05.

## RESULTS

In this clinical trial, 112 patients entered the study, 12 of which were excluded during the study. Mean age of the patients was 67.16±10.87 in the range of 46-86 years. Most patients in both groups were male. At the beginning of the trial, patients in the two groups were matched with each other in terms of age, sex, number of lesions and lesion area (Table-I).

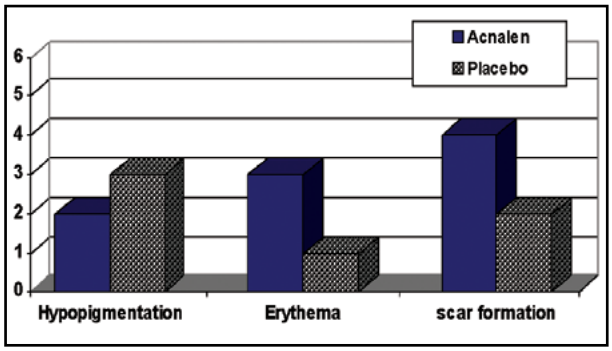


Fig.1: Observed Side effects in patients of two groups.

Table-I: Demographic finding and lesion status at the beginning of the trial.

| | Group | | |
|---|---|---|---|
| | *Acnalen* | *Placebo* | *P_V* |
| Sex (Male-Female) | 45-5 | 43-7 | 0.538 |
| Age (mean ± SD) | 67.17±10.78 | 68.86±9.69 | 0.409 |
| Lesion distribution (Face) | 7.73±1.56 | 5.39±1.53 | 0.248 |
| Lesion distribution (Scalp) | 8.87±3.38 | 8.66±3.54 | 0.763 |

Evaluating the test results of repeated measures of analysis of variance showed that the changes of average number of actinic keratosis lesions in the two treatment groups were not statistically significant (P=0.62). The mean frequency of reduction in the number of lesions was 54.79±3.8% in Acnalen therapy group and 48.60±4.5% in the placebo group; difference of reduction frequency between the two treatment groups was not statistically significant (P= 0.30).

Recovery rate of over 75% was observed in 11 (22%) cases in Acnalen group and 9 (18%) cases in the placebo group that the difference between the two treatment groups is not statistically significant (P=0.81) (Table-II)

Increase in the number of lesions (disease worsening) was observed in 2% cases in Acnalen therapy group and in 3% cases in the placebo group that the difference between the two groups was not significant in this respect (P=0.61).

The most common side effect was itching. There was no significant difference in the rate of side effects among patients of the two groups (P= 0.57). Moreover, none of the side effects led to exclusion from the study.

## DISCUSSION

The basis of treatment of actinic keratosis lesions is to remove the damaged epidermal cells before they turn into SCC.[7] Given the high prevalence of these pre-malignant lesions and importance of early treatment of them, various studies and therapeutic methods have been conducted. Destructive methods - including cryotherapy - are limited to the lesion itself and do not apply to elimination of sub-clinical lesions. Topical pharmacological treatment methods are applied to the whole area of lesions; so, in addition to their effect on the treatment of clinical lesions, they can also be effective in elimination of sub-clinical lesions.[1]

The evidences based on the effect of Retinoids on the treatment of actinic keratosis lesions are inconsistent.[1] In some studies, including issues related to Adaplen and isotretinoine, these drugs have been recognized effective. So that rate of response to treatment for Adaplen 0.1 and 0.3 percent was 62 and 66 percent respectively, and 66 percent for isotretinoine that this rate was statistically significant in both studies.[13,14] In some studies, the use of these drugs has been proposed for prevention of lesions or as adjunctive therapy with other therapies[3] and in some others, these drugs have had no clinical or prophylactic effects.[15] In our study, the effectiveness of Acnalen 0.1% gel was evaluated in treatment of actinic keratosis lesions along with cryotherapy. In our study, most patients (88%) were male which represents the effect of sunlight in appearance of actinic keratosis lesions.

Table-II: Mean of lesions count at the duration of the study

| *Lesions count* | *Group* | | |
|---|---|---|---|
| | *Acnalen* | *Placebo* | *P_V* |
| At the beginning of the Study | 7.54 ± 3.66 | 7.2 ± 3.60 | 0.641 |
| 40 days later | 4.38 ± 2.53 | 4.46 ± 2.22 | 0.867 |
| 70 days later | 3.88 ± 2.54 | 3.98 ± 2.78 | 0.852 |
| 100 days later | 3.44 ± 2.71 | 3.68 ± 2.97 | 0.674 |

Our study showed that the effectiveness of the Acnalen 0.1% gel is not significantly different compared to that of placebo in the treatment of actinic keratosis lesions. In addition, the two drugs had also no difference in terms of recovery over 75% (significant recovery). Respecting the reduction diagram of mean of lesions in both groups, it can be observed that the highest portion of reduction of the number of lesions is due to the change of the mean between the days 0 - 40 (the first visit after beginning of treatments); and obviously, it is higher than the mean change between the days 40–70 and 70–100.

So, the response to treatment observed in this study is mainly due to cryotherapy and the primary destruction of lesions; and continuation of treatment with Acnalen after cryotherapy has had no significant effect on the response to treatment. Therefore, it can be concluded that, Acnalen gel may not be suggested, at least, as a Monotherapy for treatment of actinic keratosis lesions; and also, it makes not much difference as the adjunctive treatment beside cryotherapy in the treatment response observed in the cryotherapy alone.

An increase in the number of lesions (disease worsening) was observed in 2 groups due to appearance of subclinical lesions. This result

confirmed that Acnalen alone had no prophylactic effect on new lesion along that period of time.

This result is consistent with the study by Brrera et al[3] and also Humphreys et al[15] and inconsistent with the findings of Kang et al[14] about Adaplen 0.1 and 0.3%. However, longer studies and evaluation are needed to give any opinion on the effects of prophylactic Acnalen in appearance of actinic keratosis lesions and also, evaluation of its effect in reducing the recurrence of lesions; and in most papers, a follow-up duration of at least 6 months has been suggested to investigate the effects of treatments in preventing the recurrence of lesions.[13,14] So, due to the time constraint in our study (3 months), no comment could be made whether the Acnalen treated group had a lower recurrence than the placebo group or less new lesions will appear in the Acnalen treated group (because of its potential prophylactic effects) than in the placebo group. This issue requires a larger sample size and longer follow-up of the patients.

The therapeutic effect of a drug is always measured along with its side effects. Our study showed that, first, the two groups had no significant difference in terms of side effects and; and moreover, some other complications such as hypopigmentation are related to cryotherapy and not to Acnalen. Also, the complications appeared after use of Acnalen were mild and temporary that in this respect, Acnalen regardless of its therapeutic effectiveness, is considered as a safe drug with minimal side effects.

***Study Limitations:*** Three-month follow-up seems to be insufficient for assessing the effect of the drug on reduction of recurrence rate and evaluating its prophylactic effects.

## CONCLUSION

In summary, our study showed that in the short term, use of combined treatment of cryotherapy and Acnalen 0.1% gel (as a field directed treatment) has no significant difference with cryotherapy as monotherapy in the treatment of actinic keratosis lesions.

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***Conflicts of Interest:*** The author(s) declare that they have no competing interests. There are no commercial associations, either directly or through immediate family, in such areas as: expert testimony, consulting, honoraria, stock holdings, equity interest, ownership, patent-licensing situations, or employment. There are also no conflicts for personal relationships and academic competition.

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