Actinic keratosis: sequential treatment with cryotherapy and 3% sodium diclofenac gel

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Summary

Background. Actinic keratosis (AK)s are the most frequent skin premalignant lesions and their prevalence reaches the 80% among the over 60s. Nevertheless AKs are nowadays becoming a frequent sun damage mark also in younger people. About 10-20% of subjects with AKs can develop a squamous cell carcinoma (estimate risk of 1/1000 per lesion).

Objective. Aim of this study was to evaluate the efficacy of monotherapy with liquid nitrogen cryotherapy or 3% sodium diclofenac gel, versus their association.

Methods. 175 patients with AKs located on face and scalp were enrolled and divided into 3 different treatment groups. Group A was treated with 3% sodium diclofenac gel, group B received combined therapy with cryotherapy plus 3% sodium diclofenac, group C received cryotherapy.

Clinical evaluation was performed every 6 weeks for 6 months.

Results. Group B had the most effective therapy, reporting 95.3% of improvement compared to 70% of group A and 87.1% of group C. Moreover, from patients evaluation of aesthetic outcome, time consuming and discomfort from treatment, combined therapy resulted largely preferred.

Conclusions. Combined treatment with cryotherapy and 3% sodium diclofenac gel represents a very suitable treatment option for AKs, as resulted from our study, either from the doctor, or the patients point of view.

KEY WORDS: actinic keratosis; liquid nitrogen cryotherapy; 3% sodium diclofenac gel; treatment.

Introduction

Actinic keratoses (AKs) are the most frequent premalignant lesions appearing on the skin surface, composed of proliferative, transformed keratinocytes that develop as a result of chronic UV exposure (1). AKs are generally diagnosed clinically and present as asymptomatic or slightly itchy rough patches or papules with erythema and scaling, on sun-exposed skin, predominantly in older, fair-skinned individuals. Histologically, AKs are characterized by keratinocytes atypia in the deeper layers of the epidermis, with defective cellular maturation of the upper layers (2). Epidemiological, clinical, histopathological and molecular studies have demonstrated that AKs represent the early stage of a transforming biological process ranging from carcinoma in situ and possibly leading to invasive spinal cell carcinoma (SCC) (3). Although the risk of invasive SCC from a single, specific lesion is relatively low, the evidence from many histological reports demonstrates that 60 to 80% of SCCs develops from AKs lesions, especially in presence of certain clinical features, such as large size, ulceration or bleeding. Owing to difficulties in predicting which AK will progress to SCC, early diagnosis and treatment are essential, although sun damage prevention remains the most important procedure (1). Moreover patients with extensive solar damage, advanced age, and immunosuppression are more prone to get AKs and possibly SCCs, so they have to be strictly followed-up and promptly treated when necessary. Treatment options for AKs include physical methods to ablate individual lesions and methods direct to the entire dysplastic field (2). Physical treatments may clear AKs with one procedure, but may be associated with pain and anxiety related to aesthetical discomfort and to the possibility of repeated procedures for clearing multiple lesions. Topical therapies, applied for several weeks, are appropriate for new or recurring lesions; they may reveal and clear subclinical lesions (4). Thus, the choice of treatment depends on lesions number and location, on the individual compliance and aesthetical expectation. Sometimes combining multiple approaches may result more effective.

In the present study, following previous experiences of
our and other groups (5-7), we compared the efficacy of monotherapy with liquid nitrogen cryotherapy or with 3% sodium diclofenac gel, versus their sequential association in the treatment of AKs.

**Materials and methods**

This was a 1-year prospective study of patients affected by AKs located on face and scalp, attending our out-patients clinic, at the University of Naples Federico II. Subjects with homogeneous clinical pattern were enrolled during 6 months, treated and followed up for 6 months. Ethical approval was obtained from the local Ethical Committee. All patients were visited by the same doctor and, following informed, written consent, each participant was required to answer a questionnaire (Appendix 1) aimed at establishing personal medical history of AKs, SCCs and their previous treatment, immunosuppressive therapies or comorbidities (8). Exposure to UVR was also documented. After the screening visit (T0), patients were randomized in three treatment groups and started therapy. Thereafter, regular clinical follow up was performed every 6 weeks (T1, T2, T3, T4, respectively corresponding to 6, 12, 18 and 24 weeks after randomization and therapy initiation).

Group A was treated in monotherapy with 3% sodium diclofenac gel (Solaraze®, Almirall, Barcelona, Spain): patients were instructed to apply the gel, on lesions area, twice a day for 12 weeks. Group B received combined therapy: cryotherapy first (7 + 7 seconds of application) and, 2 weeks after the cryotherapy session, patients were asked to start 3% sodium diclofenac gel application, twice a day, on the same lesions area for 8 weeks. Group C patients had their singular AKs lesions treated by cryotherapy (as described for group B) with 2 liquid nitrogen sessions in a month. Thereafter follow-up visits were performed for 5 months.

At the first visit, before starting therapy, a morphological evaluation was performed by the doctor and a total clinical score was attributed to each patient at every visit, considering the number of lesions and their clinical features. The grading attributed to the number of lesions was: 1 (n <5), 2 (n =5-10), 3 (n =11-20), 4 (n >20). A 4-point arbitrary scoring scale (0: absent, 1: mild, 2: moderate, 3: severe) was used to define lesions clinical features, such as hyperkeratosis, erythema and erosion and, together with the value assigned to the number of lesions, represented the total clinical score (Table 1). Moreover, analyzing patients answers about life style and sun exposure behaviour (occupation, hobbies, holidays, sun lamp and photoprotection), the risk of developing sun induced skin lesions was calculated and expressed in an arbitrary scale from 3-13 (see Appendix 1 for score grading legend). This scale could not start from zero because nobody leaving in Naples area completely avoid sun exposure. In addition, itch, the main symptom referred by patients, was recorded with an arbitrary 4 point grading system (0: absence of itch; 1: mild itch; 2:...
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moderate itch; 3: severe itch) (Table 1). Statistical analysis, to evaluate clinical score differences, was performed using GraphPad Prism 4.0 (GraphPad Software Inc, La Jolla, CA). Student’s t test was used to calculate statistical differences.

Results

175 patients were enrolled in the study (Table 1), 168 (96%) patients completed the study; 4 (2.3%) patients drop out because of adverse reactions such as erythema, itch and erosion; 3 (1.7) patients were lost during the follow-up.

At baseline, the mean number of lesions corresponded to 2.0 (scoring system from 1 to 4, as reported in materials and methods) for the group A, 2.6 for the group B and 2.3 for the group C (average about 10 AKs per person, equally distributed in the three groups; Table 1). The mean clinical features score (hyperkeratosis, erythema and erosion) was 3.2 for the group A, 3.7 for the group B and 3.1 for the group C. Considering both parameters, number of lesions and clinical features, a total clinical score was assigned to each single group: 5.2 to group A, 6.3 to group B and 5.4 to group C (Table 1).

Sun exposure risk was similarly represented in the three groups and was codified as 8.6 in the group A, 7.6 in the group B and 7.4 in the group C. Moreover itch, evaluated at the enrollment time, resulted: 1 in the group A, 1.3 in the group B and 1.2 in the group C (Table 1).

Positive history of cutaneous carcinoma (either SCC or basal cell carcinoma) was reported in 33, 27 and 31% of patients, respectively enrolled in the group A, B, or C and, among previous treatments, most frequently cryotherapy was referred.

After 6 months from the enrollment, all the three groups of patients showed clinical improvement (Figure 1). Group A treated with 3% sodium diclofenac gel twice a day for 12 weeks showed an improvement of 70% with good lesions regression, and, at the last follow up after therapy discontinuation (T4: 24 weeks from the enrollment), no lesions recurrence was observed. In this group the baseline total clinical score (calculated at T0) was 5.2, at the end of the drug application time (T2) was 1.9, whereas at the last follow up was 0.6 (Figure 2); a mean decrease of 4.6 was observed in this group from the start to the end of the study (Figures 2, 3).

The group B, treated once with cryotherapy (7 + 7 seconds) and two weeks after with 3% sodium diclofenac gel application for 8 weeks, showed almost complete remission (95.3% of improvement). During the treatment period a marked progressive improvement was recorded: the initial (T0) clinical score of group B was 6.3, at the end of the application time was 2, at the last follow up (T4) was 0.3 (Figure 2); a mean decrease of 6 was observed from the start to the end of the study (Figures 2, 3).

Group C treated with cryotherapy (7 + 7 seconds, one session every two weeks in one month), at the last follow up (T4) showed 87.1% of improvement. In this

Figure 1 - Clinical pictures before (T0) and after treatment (T4) of three patients representative for the three treatment groups (from the left to right respectively group A, B and C).
group the initial clinical score was 5.4, after the second treatment was 2.1, at the last follow up was 0.7 (Figure 2). A mean decrease of 4.7 was observed from the start to the end of the study (Figures 2, 3).

Furthermore, concerning to itch, a general decrease was observed from T0 to T4, in particular it was of 83% in the group A, of 80% in the group B and of 79% in the group C.

Recurrence, during the study period was rare (1.7%) and was observed only in the group C: 3 out of 65 patients (4.6%) manifested relapses of lesions previously treated.

Discussion

The sequential treatment with cryosurgery followed by diclofenac sodium 3% gel for 2 months was well tolerated and induced greater clinical improvement, efficiently treating the singular clinical lesions and the cancerization field, compared to monotherapy with diclofenac sodium 3% gel for 3 months or two repeated liquid nitrogen applications.

Owing to difficulties in predicting which AKs will progress to SCC, the general rule is to treat all AKs.

Therapeutical options used in the clinical practice are various and depend especially on the number of lesions, age of patient, history of skin cancer and tolerability of therapy modality.

AKs treatment is usually classified as lesion-directed or field-directed therapy. The most common lesion-directed treatment is liquid nitrogen cryotherapy which leads to lesions physical destruction (9). It has been the therapeutic modality preferred by dermatologists, because it has an impressive short-term effect, it is easy and office-based and does not require anesthe-
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... sia. Moreover cryotherapy can be used for treating few as well as multiple lesions, resulting in the most cost-effective treatment modality (10), although, because it does not affect perilesional skin, significant recurrence has been observed (11). Field cancerization is treated with ablative methods, such as dermabrasion and chemical peels, as well as photodynamic therapy, creams and gels containing active components that lead to elimination of transformed cells. Topically applied pharmacologic therapies, such as 5-fluorouracil, imiquimod, diclofenac and the newest ingenol mebutate (12), are generally used for several weeks and may cause localized inflammation, with erythema, burning sensation and ulceration, possibly compromising patient’s compliance (12). Accumulating evidence from preclinical research supports that the proposed mechanism of diclofenac sodium 3% gel may include inhibition of cyclo-oxygenase 2 (COX-2) and angiogenesis, other than induction of apoptosis (13). Current approaches to the management of AKs use both lesion-directed and field-directed methods as a strategy to increase the overall treatment success (12). From clinical practice, the evidence of better results with combined therapy has emerged over the past years (6, 13). With our study, we wanted to reinforce this concept with a comparative examination of monotherapy with liquid nitrogen cryotherapy or 3% sodium diclofenac gel, versus their association, on the basis of clinical parameters registrations and patients experience. Our findings are in line with Berlin et al. (6) showing that cryotherapy followed by diclofenac 3% gel represents the best way for treating AKs in terms of efficacy, recurrence and costs. Instead, Mastrolonardo et al. treated 29 AKs patients resistant to cryotherapy with diclofenac 3% gel twice daily for 12 weeks and, at the end of treatment, managed only residual lesions with liquid nitrogen. They deemed that this was a very effective approach to treat refractory AKs. In our experience the two monotherapy groups had the same clinical improvement, considered as the difference between clinical score reported at T4 and T0, showing similar efficacy with different time-response curve (Figure 2). Group A improved more slowly and constantly compared to group C that reported a prompt response after cryotherapy, joining a plateau with further slight amelioration (Figure 2). In the group B, clinical improvement was the most impressive (Figure 3) and was represented by a time-response curve showing rapid clinical score decrement, after the singular cryotherapy session, maintained by the consecutive diclofenac gel application. Furthermore, concerning patients compliance, the sequential treatment resulted very well tolerated because liquid nitrogen discomfort was limited to one session and gel application time was shorter. As resulted from literature revision, patients consider their quality of life (QoL) affected by AKs (14) and diclofenac gel therapy was able to significantly improve it (15). In our study, the highest compliance and satisfaction for aesthetic outcome was reported in the sequential therapy group (B). Probably a bigger study population would confirm the trend emerged from the present study, and a prolonged follow up period would highlight eventual recurrence. However, the increased lifespan, and the reiterated incoherent sun exposure attitude of modern and industrialized population (week-end exposure, sun bathing, sun beds) will enhance the risk of developing more premalignant and malignant skin lesions. Easy, effective, small time consuming and well tolerated treatments are certainly the objective of pharmaceutical investigations, but we do not have to forget how to use and to combine consolidated products and procedures.

References

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the treatment of actinic keratoses postcryosurgery.

Appendix 1 - Questionnaire: Actinic keratosis

Name and surname initials:
Sex: M F Age: D.O.B.
Fitzpatrick skin type classification (for doctor): I, II, III, IV
Occupation

1. Light exposure risk score from reported life style: 3-13
How many years Do/Did you work outdoors? 1(0 yrs); 2(<10 yrs); 3(>10yrs)
Do you enjoy your free time outdoors? 1(<3h/w); 2(6-9 h/w); 3(>9 h/w)
Do/Did you go for holidays to very sunny places? 1 (w/ys); 2 (w/ys); 3 (w/ys); 4 (w/ys)
Do/Did you use sun beds? 0(no), 1(yes)
Do you use sun protection? 0(no); 1 (sometimes); 2 (always)

2. Clinical picture
Number of lesions (#): 1 (n<5), 2 (n=5-10), 3 (n=11-20), 4 (n>20)
Locations: face, neck, scalp, arm, hand, trunk, other
Lesions score: 1-9
hyperkeratosis (1: mild, 2: moderate, 3: severe)
erthema (1: mild, 2: moderate, 3: severe)
erosion (1: mild, 2: moderate, 3: severe)
Itch: (absence of itch=0; mild itch=1; moderate itch=2; severe itch=3)

3. Therapy
Previous treatment:
1. Topical therapy
   - 5-fluorouracil
   - Sodium diclofenac
   - Topical steroids
   - Imiquimod
   - Retinoids
   - Other (keratolytics, emollients, etc.)
2. Photodynamic therapy
3. Cryotherapy
4. Curettage
5. Radiotherapy
6. Surgery
Adverse reactions: ………………………………………………………………………………………………………………………

4. History of skin cancer:
Have you ever had a skin cancer? Yes No
At what age?
If yes, are you able to say if it was:
Melanoma Where was it located?
Squamous cell carcinoma How was it treated?
Basal cell carcinoma Has there been any recurrence of the skin cancer?

Current treatment (randomization group):
A. Sodium diclofenac 3% o solaraze
B. Cryotherapy + Solaraze
C. Cryotherapy