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RESEARCH ARTICLE

Treatment of Actinic Keratosis by Topical 25%Podophyllin Solution

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Abstract

Background: Actinic keratoses (AK) are most common type of in situ SCC of the skin among light-skinned individuals. And it is not uncommon in Iraqi population. Numerous modalities of treatment are available. Podophyllin is an antimitotic and caustic agent that has been used in treatment of genital warts.

Objective: To test the effectiveness and safety of topical 25% podophyllin solution in treatment of actinic keratosis.

Patients and Methods: Twenty patients with actinic keratosis enrolled in this open labeled interventional study that had been conducted in Department of Dermatology-Baghdad Hospital, Baghdad, from January 2010 to October 2011.

History and examination were carried for each patient and all related points were recorded.

Skin phototype was established for all patients according to Fitzpatrick's classification. Actinic keratoses were identified regarding their number, type, and site, morphology of the lesion, size, color, and surface.

All the following conditions were excluded from the study, pregnancy, immunosuppressant conditions like organ transplantation, lesion near the eyelids, and lesion more than 1.5 cm in diameter. Biopsies were done as confirmatory test for some lesions.

The lesions of actinic keratosis were treated with 25% topical podophyllin solution once weekly for 6 weeks to evaluate the response and side effects of the treatment, And for every 3 months for 6 months after clinical cure to check for any sign of recurrence of the lesions.

Results: All the twenty patients with actinic keratosis completed the study: 15 (75%) males and 5 (25%) females with males to females ratio 3:1, their ages ranged from 26 - 80 with a mean (57.25 ± 14.18) years, and the duration of the disease ranged from 2 months to 10 years with a mean (4.029 ± 4.5867) years. The total numbers of lesions were 120 lesions their size ranged from 5-15 with a mean (8.2 ±.2.19) mm. The total number of podophyllin applications ranged from 3–6 with a mean (4.3 ± 0.80) sessions.

Regarding the occupation of patients was mainly outdoors in 14 (70%) patients, indoors in 6 (30%) patients. Regarding skin phototypes, 12 (60%) patients were of type IV and 8 (40%) patients were type III. The lesions were distributed mainly on the bald scalp, forehead, cheek, nose, and dorsum of the hands.

One hundred and seventeen from 120 of all treated lesions in 20 patients showed complete clinical cure (97.5%) in 3-6 sessions. While 3 (2.5%) of all

treated lesions showed partial response with 6 sessions. All the patients did not show clinical recurrence, for up to 6 months follow up.
No evidence of systemic side effects was seen and this had been confirmed clinically and by laboratory tests during the sessions and 1 month later. Local side effects like irritation, burning, and slight pain were noticed.

Conclusions: Topical 25% podophyllin solution is a new therapeutic modality in treatment of actinic keratosis which gave 97.5% cure rate within short time.

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INTRODUCTION

Actinic keratoses (AK), also known as solar keratosis, are most common type of in situ SCC of the skin among light-skinned individuals. These lesions are confined to the epidermis and develop solely on sun-damaged skin. [1] AK has been recognizing and eventually classified as a "precancerous" skin lesion that is common in the elderly. [2] Ackerman suggested AK/AC is not a "precancerous" skin lesion, but, in fact, SCC in situ. [3] AK is the initial manifestation of a continuum of clinical and histopathological abnormalities that progress into invasive SCC. [4] The risk of progression to invasive SCC has been estimated to range from 0.25% to 20% per year. [5] Early data suggest that actinic keratoses may also progress to basal cell carcinoma. [6] Increased sun exposure and higher-intensity exposure increase the chance of actinic keratosis development. Immunosuppression following organ transplantation dramatically increases the risk of developing actinic keratoses; however, actinic keratoses do not occur without sun exposure. [7] In Iraq, actinic keratosis is not uncommon problem although people are mostly III, IV skin types. [8] DNA analysis of the cells within AK shows characteristic UV-induced mutations in key genes, including *TP53* and deletion of the gene coding for p16 tumor suppressor protein. [9,10]
AK appears as an ill-defined, subtle, erythematous macule with a slightly hyperkeratotic surface on sun-exposed areas of the head and neck, forearms, hands, and upper back. Lesions can be multiple, usually less than 1 cm in diameter. AKs may appear pigmented with a tan-brown color, as well as red or skin color with no well-defined borders. In addition, the surface of AKs has a dry, firmly adherent scale with a rough, sandpaper-like consistency. The key to clinical diagnosis on physical examination is the sandpaper-like sensation felt on touching the surface of these persistent skin lesions on sun damaged skin. There are many different clinical forms other than the earlier-mentioned classical one, these include: atrophic, keratotic popular, verrucous/papillomatous, hyperplastic, pigmented, solitary lichenoid proliferative multiple, acantholytic, spreading pigmented, Cutaneous horn, and conjunctival AK is termed pinguecula or pterygium. [3,4,11,12]
Treatment of AK consists of either surgical destruction of the lesions such as excision, curettage, cryosurgery, and Cosmetic resurfacing procedures include medium and deep chemical peels, dermabrasion, and ablative laser resurfacing.[13, 14,15]. Medical therapy begins with educating the patients to limit sun exposure as much as possible put sunscreens and they also must wear adequate protective clothing daily. [16] The Food and Drug Administration (FDA) have approved 5 medications for the treatment of actinic keratoses. These are topical 5-fluorouracil (5-FU) [17] 5% and 3.75% Imiquimod cream [18] topical diclofenac gel [19] PDT with topical delta-aminolevulinic acid [19]. And Ingenol mebutate gel (Picato) was approved by the FDA for actinic keratosis in January 2012 as a 2-3 day course of therapy. [20]

In Iraq, topical zinc sulphate was found to be an effective treatment of a wide variety of skin disorders such as: basal cell carcinoma [21] xeroderma pigmentosa [22] Cutaneous leishmaniasis, [23] plane warts, [24] Most recently Zinc sulphate solution 25% was reported as an effective topical therapy in the treatment of actinic keratosis. [25]

Podophyllin: Is the dried resin extracted from the roots and rhizomes of *Podophyllum peltatum* known as American mandrake, May apple, Ducks' foot and Indian apple. It is an antimitotic and caustic agent, a lipid-soluble compound with cytotoxic properties that easily crosses cell membranes lead to inhibit cell mitosis and DNA synthesis by reversibly binds to tubulin; the protein subunit of the spindle microtubules, thereby preventing polymerization of

tubulin into microtubules, cell division is arrested, and other cellular processes are impaired. It often causes local necrosis and death of tumor cells and erosion of the tissues. [26, 27, 28] It blocks oxidation enzymes in tricarboxylic acid cycle, so it will interfere with nutrition of cells. It inhibits axonal transport, protein, RNA, and DNA synthesis. It is also inhibits mitochondrial activity and reduction of cytochrome oxidase activity. [29,30,31] Podophyllin is indicated for the treatment of condyloma acuminatum (venereal warts), [32] oral hairy leukoplakia, [32], juvenile papilloma of the larynx, [33] Molluscum contagiosum. [34]

There is a local side effects associated with topical podophyllin such as erythema, tenderness, pruritus, burning, erosions, pain, and swelling. [26] There is systemic side effects were if extensive podophyllin treatment used for large area, sub-dermal injection or ingestion. [31, 33]

The aim of present work is to report the effectiveness of 25% topical podophyllin solution in the treatment of actinic keratosis.

Patients and method:

Twenty patients with actinic keratosis enrolled in this open labeled interventional study that had been conducted in Department of Dermatology-Baghdad Hospital, Baghdad, from January 2010 to October 2011.

Full history from each patient was taken regarding age, sex residence, occupation, habitual use of sun protective clothes or sunscreen, history of previous similar lesions and treatments used, predisposing medical conditions such as xeroderma pigmentosa, epidermodysplasia verruciformis, albinism, organ transplant, drug history such as cytotoxic and systemic corticosteroids, duration of lesions and associated symptoms such as pain, local tenderness, itching or burning sensation.

Skin phototype was established for all patients according to Fitzpatrick's classification. Patients were examined for the presence of signs of sun damage judged by presence of rhytids, dyspigmentation, poikiloderma, lentigines, skin thinning, and/or telangiectases. Actinic keratosis were identified regarding their number, type site, morphology of the lesion, size, color, smooth, scaly, verrucous surface.

Patients were examined for the presence of regional lymphadenopathy. All the following conditions were excluded from the study, pregnancy, immunosuppressant like organ transplantation, lesion near the eyelids, and lesion more than 1.5 cm in diameter unless proved by biopsy to be AK. Diagnosis was mainly clinical; biopsy was done as confirmatory test in some lesions.

Formal consent was taken before the start the therapy, after full explanation about the nature of the disease, course, the procedure of treatment, follow up, prognosis and the need for pre and post treatment photographs. Also, ethical approval was given by the Scientific Council of Dermatology and Venereology- Iraqi Board for Medical Specializations.

The lesions of actinic keratosis were treated with 25% topical podophyllin solution once weekly for 6 weeks, and patients were seen every week for 6 week to evaluate the response and side effects of the treatment, and for every 3 months for 6 months after clinical cure to check for any sign of recurrence of the lesions.

Descriptive statistics, including frequencies and proportions for categorical data and means, standard deviations, and medians for continuous data, were calculated

Preparation of topical 25% Podophyllin solution and the way of use Podophyllum Resin 25% Topical Solution prepared by mixing 25 grams of the alcohol-soluble extract of podophyllum resin in 100 ml tincture benzoin and alcohol. The solution was applied by a wood stick applicator and the lesion was covered with thin layer of solution. The amount used in each session depends on size of lesion but always not exceeding 0.5ml. The solution was allowed to dry in approximately 3 minutes and patients were instructed to wash off it after 4 hours. The solution was applied once weekly for maximum of 6 weeks and the number of applications depend on rate of response of the lesions. [24]

Results:

All the Twenty patients with actinic keratosis completed the study: 15 (75%) males and 5 (25%) females with males to females ratio 3:1, their ages ranged from 26 - 80 with a mean (57.25 ± 14.18) years. And the duration of the disease ranged from 2 months to 10 years with a mean (4.029 ± 4.5867) years. The total numbers of lesions were 120 lesions their size ranged from 5-15 mm with a mean (8.2 ±.2.19) mm. The total number of podophyllin applications ranged from 3–6 with a mean (4.3 ± 0.80) sessions.

Regarding the occupation of patients was mainly outdoors in 14 (70%) patients, indoors in 6 (30%) patients. Regarding skin phototypes, 12 (60%) patients were of type IV and 8 (40%) patients were of type III. The type of lesions were mainly pigmented scaly erythematous. The lesions were distributed mainly on the bald scalp, forehead, cheek, nose, dorsum of forearm and hands. (Table 1)

One hundred and seventeen from 120 of all treated lesions in 20 patients showed complete clinical cure (97.5%) in 3-6 sessions. While 3 lesions from all treated lesions showed partial response in 6 sessions (2.5%). All the patients did not show clinical recurrence, for up to 6 months follow up.

No evidence of systemic side effects was seen, and this had been confirmed clinically and by laboratory tests during the sessions and 1 month later. Local side effects like irritation, burning, and slight pain were noticed.

Figure 3-A: Actinic keratosis on tip of the nose and squamous cell carcinoma on the cheek before podophyllin application

Figure 3-B: The same patient above showing clearance of AK of the nose, and SCC, of the cheek by 6-sessions of podophyllin application

Figure2-A: Multiple actinic keratosis-foreheads before podophyllin application.

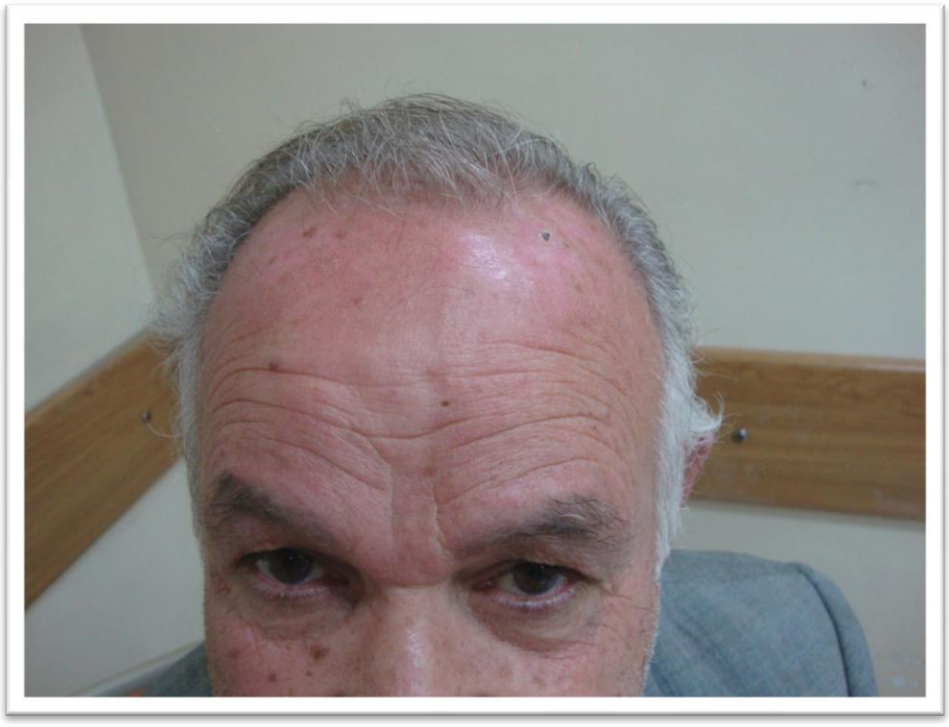

Figure2-B: The same patient above 4-sessions of podophyllin application.

Table 2: Sites affected and number of lesions in 20 patients with actinic keratosis

Site of the lesions	*No. of patients*	*No. of the lesions*
Scalp	**1**	**4**
Nose. Forehead	**2**	**3**
Nose. Cheeks	**3**	**4**
Nose, cheeks forehead	**4**	**5**
Nose, cheeks.	**5**	**3**
Nose, cheeks.	**6**	**4**
Scalp, forehead	**7**	**5**
Scalp. Forehead	**8**	**5**
Scalp, face	**9**	**6**
Forearm, hands	**10**	**3**
Temple, face	**11**	**4**
Nose, forehead	**12**	**3**
Face, hands	**13**	**6**
Face	**14**	**3**
Nose, cheeks.	**15**	**3**
Face, hands, scalp	**16**	**22**
Scalp	**17**	**4**
Face	**18**	**10**
Scalp	**19**	**4**
Forehead, face, hands.	**20**	**24**
Total	**20 patients**	**120 lesions**

Discussion

Actinic keratosis is a major health problem among many countries. Its incidence is striking increased in countries with latitudes close to the equator. [(1)] In Iraq although most people have skin types III, IV still actinic keratosis is not uncommon problem. [(8)]

Chronic UV light exposure is considered to be the most important pathogenic factor in the development of AK. Organ-transplant recipients, other immunocompromised individuals, albinos, and persons with EV and XP have an increased propensity to develop AKs. [(35)]. Treatment of AKs is indicated to avoid any chance of progression to invasive SCC. Therapy of this disease is also warranted to minimize symptoms in affected patients with painful and pruritus AKs and for cosmetic reasons. [(35, 36, 37)]

In general treatment of AK based on the number of lesions present and the efficacy of the treatment, persistence of the lesion(s), age of the patient, history of skin cancer, and tolerability of the treatment modality. The advantage of medical therapy has being able to treat large areas with many lesions. [(38)]

The Food and Drug Administration (FDA) have approved 5 medications for the treatment of actinic keratoses. These are topical 5-fluorouracil (5-FU) [(17)] 5% and 3.75% Imiquimod cream [(18)] topical diclofenac gel [(19)] PDT with topical delta-aminolevulinic acid [(19)]. And Ingenol mebutate gel (Picato) was approved by the FDA for actinic keratosis in January 2012 as a 2-3 day course of therapy. [(20)] These topical agents are costly and treatment will be associated with

significant side effects [39]. Most recently Zinc sulphate solution 25% was reported as an effective topical therapy in the treatment of actinic keratosis. [25].

These FDA approved topical therapeutic modalities used in the treatment of actinic keratosis have many disadvantages include: lengthy courses, costly, with temporarily disfiguring with erythematous ulceration and crust formation [39]. As Imiquimod applied 2-3 times a week for up to 4 months, [40] diclofenac 3% gel applied twice daily for 3 months [41] and 5-FU application twice daily for 4 weeks.

In the present work, topical 25% podophyllin solution had been used in treatment of actinic keratosis in the head and neck, for single and multiple actinic keratoses with cure rate 97.5% in 3-6 sessions. Within not more than 1.5 months It is gave a high cure rates, no relapse, recovery with short time, no post treatment scarring and no systemic and minimal topical side effects. These results are comparable to results of 25% topical zinc applications. [25]

Mechanism of the action of podophyllin cannot well be elucidated, but we can speculate this drug act through its main mechanism of actions as following: it is an antimitotic, caustic and antiviral agent, a lipid-soluble compound with cytotoxic properties that easily crosses cell membranes lead to inhibit cell mitosis and DNA synthesis by reversibly binds to tubulin. So cell division is arrested, and other cellular processes are impaired, [26, 27, 28] in addition to its other effects. [29, 30, 31] accordingly when podophyllin therapy compared with other treatment we can summarize the following: most therapies should be applied on daily bases, takes longer duration for recovery, associated with many and even could be severe side effects, costly, and with low cure rates. While podophyllin is applied once a week, recovery within short times and gave a high cure rate in comparable to excision, curettage and electrodessication and radiotherapy cure rates.

In conclusions 25% topical podophyllin solution was found to be an effective mode of therapy in clearing actinic keratosis with cure rate 97.5% of patients and with short time compared with other therapies.

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