

Comparative Study of Cryotherapy versus Trichloroacetic Acid Chemical Peels in the Treatment of Actinic Keratosis

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ABSTRACT

Actinic keratosis (AK) is cutaneous neoplasm which is including of expansion of cytologically unusual epidermal keratinocytes that grow in response to prolonged exposure to ultraviolet radiation. Since some percentage of AK will develop to non-melanoma skin cancers, their treatment is recommended. The study aimed to evaluate the clinical effectiveness of cryotherapy in comparison to topical 25% trichloroacetic acid (TCA) chemical peels in the treatment of AK. A comparative therapeutic study was conducted on 44 patients with AK who attended Erbil dermatology teaching center in Erbil city of Kurdistan Region-Iraq. Patients were randomly allocated into two groups: Cryotherapy treatment with liquid nitrogen every 2 weeks and TCA peels every 2 weeks, and the response was controlled on follow-up by taking photos. Patient's age ranged from 40 to 80 years; they were analyzed for 24 weeks. Good response rate was seen in 72.8% of the cryotherapy group and 40.9% of TCA group and this was statistically significant ($P = 0.02$). Cryotherapy was more effective than TCA in the treatment of AK.

Keywords: Actinic keratosis, Cryotherapy, Squamous cell carcinoma, Trichloroacetic acid

1. INTRODUCTION

Actinic keratosis (AK) represents *in situ* dysplasia resulting from sun exposure. It is found chiefly on the chronically sun-exposed surfaces of the face, ears, balding scalp, dorsal hands, and forearms (James *et al.*, 2016). Lesions vary in size from <1 mm to over 2 cm and are usually asymptomatic (Girish *et al.*, 2016). AK initially appears as a tiny, palpable lesion on normal sun-exposed skin that gradually enlarges and becomes red and scaly. The overlying scale may be extended to the point that markedly exophytic cutaneous horns are produced (Fitzpatrick and Morelli, 2011) although the rate of progression of an individual AK to invasive squamous cell carcinoma (SCC) has been estimated to be low

(<0.1%) (Salasche, 2000). AKs are clinically important lesions, not only due to their potential to develop into SCC but because they are one of the strongest predictors that an individual may subsequently develop melanoma or nonmelanoma skin cancer (Zhang *et al.*, 2010). Various risk factors have been identified for the expression of AKs. The two major ones are individual susceptibility and cumulative ultraviolet radiation exposure. One of the most important susceptibility risk factors is age. Another individual risk factor is immunosuppression, because it is known that organ transplant recipients and patients receiving certain chemotherapy agents and possibly even biologic therapies are at increased risk of developing AKs and SCCs (Duncan *et al.*, 2011).

Treatment modalities for AKs can be broadly divided into: Lesion-Targeted therapies and field therapies (Duncan *et al.*, 2011).

1.1. Lesion-Targeted Therapies

- Liquid nitrogen cryotherapy
- Curettage with or without electrosurgery
- Shave excision.

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1.2. Field Therapies

1.2.1. Topical

- 5-fluorouracil cream and solution
- 5 % imiquimod cream
- 3% diclofenac gel.

1.2.2. Procedural

- Cryopeeling
- Dermabrasion
- Medium-depth chemical peel
- Deep chemical peel
- Laser resurfacing
- Photodynamic therapy (Duncan *et al.*, 2011).

Cryosurgery is the controlled application of cold to cause tissue damage. It can be used to treat both benign and malignant skin conditions. With cryosurgery, the degree of tissue damage is controlled to destroy the target lesion with minimal damage to normal surrounding tissue (Fitzpatrick and Morelli, 2011). Liquid nitrogen is the cryogen of choice in dermatology. It is easy to store and use, environmentally friendly, non-flammable, and inexpensive (Duncan *et al.*, 2011). It is the liquid state of gaseous nitrogen. It is extremely cold, boiling at minus -198.8°C . (-320.4 F). It is necessary to store and transport it in special flasks (The British Association of Dermatology, 2008). Cryotherapy is believed to cause cell death by ice crystals formation in the cell damage cellular components (James *et al.*, 2016). Chemical peeling is the application of a chemical agent to the skin, which causes controlled destruction of a part or entire epidermis, with or without the dermis, leading to exfoliation, and removal of superficial lesions followed by regeneration of new epidermal and dermal tissues (Khunger and Iadvl, 2008). Trichloroacetic acid (TCA) in concentrations of 10–25% is used extensively as a superficial peel. The depth of injury is related to the concentration and the number of applications, with repeated coats of a low-concentration TCA leading to greater penetration (James *et al.*, 2016). Chemical peels can eliminate AKs and may be able to provide prophylaxis for a prolonged time period (Kligman *et al.*, 1985). Chemical peels with TCA should be avoided in case of presence of either active infections like (bacterial, viral and fungal) or presence of preexisting dermatological diseases like psoriasis and atopic dermatitis and also when there is history of photosensitizing drug reaction.

2. MATERIALS AND METHODS

A comparative study comparing two types of therapy in the treatment of AK was conducted in the Erbil dermatology

teaching center in Erbil city of Kurdistan Region-Iraq, from March 2018 to January 2019. The study population were 44 patients diagnosed clinically as having AK.

Lesions larger than 3 mm in its greatest diameter on face and scalp with age over 20 years were included. Males and females had the same chance to be included in this research study. Demographic data were collected from patients by direct interview including name, age, residence, occupation, number, site, duration of the lesion, grade of the lesion, type of skin, history of sun exposure, and history of other skin disease and others were recorded in the predesigned questionnaire. Lesions were graded according to the following criteria (Thai *et al.*, 2004).

- Grade1. Mild-slightly palpable lesions, better felt than seen
- Grade2. Moderate-moderately thick AK, easily felt and seen
- Grade3. Severe-very thick and/or obvious AK (Thai *et al.*, 2004).

The following lesions were excluded: (1) Grade three lesions, (2) lesions <2 mm in their greatest diameter, (3) lesions not located on face and scalp, (4) lesions were small in size and multiple that definitive borders cannot be determined, (5) patients who received other treatment modalities or have previous history of radiotherapy or chemotherapy, (6) immune-deficient patients (cancer chemotherapy, systemic corticosteroid, renal transplant status, etc.), (7) patient who have history of keloid formation, and (8) patient with contraindication criteria for cryotherapy and TCA chemical peels. Patients were randomly allocated to one of the two groups:

2.1. Cryotherapy Group

Twenty-two patients were included; they were treated by cryotherapy by applying a handheld (-198°C) liquid nitrogen unit using the direct open spray technique. Spray gun was held perpendicular to the lesion, at a distance of 1–2 cm so that uniform freezing of the lesion with a 1–2 mm rim of frozen tissue, beyond the marked outline could be achieved. We used a single timed freeze-thaw cycle. The freeze time was 10 s. Patients were followed every 2–3 weeks apart.

2.2. TCA Acid Group

Twenty-two patients were included; TCA 25% was prepared by adding 25 g of TCA to 75 ml of distilled water which was produced by Automatic Water Still machine that reserves water automatically also it has to overheat safety sensor, its sterile pathogen free. Then, it was applied on the lesion with

cotton-tipped applicator or gauze. Left in its place till frosting was appeared. Then, the patients were asked to wash their face with cold water until the burning sensation subsides. Patients were followed up every 2–3 weeks apart.

At last, both groups were advised to avoid sunlight and apply broad-spectrum sunscreen.

Both groups received a maximum of four to five treatment sessions. The response of each lesion was clinically classified by investigators as a good response when there is the complete disappearance of the lesion, moderate response when there is partial disappearance and poor response when the lesion is still present regardless of size.

The study was approved by the Ethics Committee of the college of medicine; Hawler Medical University and permission letter from Erbil directorate of health were obtained. The purpose of the study carefully explained to each participant, and informed verbal consent was obtained from them. Statistical Package for the Social Sciences, SPSS, version 23 was used for data analysis.

3. RESULTS

There was no statistically significant difference between the two groups regarding their age ($P = 0.1$). No significant differences were observed between the patients treated with cryotherapy and the patients treated with TCA regarding gender ($P = 0.2$), occupation ($P = 0.1$), and residence ($P = 0.2$) [Table 1].

No significant differences were observed between the patients treated with cryotherapy and the patients treated with TCA regarding AK disease duration ($P = 0.4$), grade of lesion ($P = 10$), skin phototype ($P = 0.1$), itching ($P = 0.2$), and skin cancer ($P = 0.6$). The outdoor occupation was significantly higher among AK patients treated with TCA in comparison to patients treated with cryotherapy ($P = 0.002$) [Table 2].

Although no significant differences were observed between the patients treated with cryotherapy and the patients treated with TCA regarding a number of sessions ($P = 0.1$), 3 (13.6%) the patients treated with more than 5 sessions of cryotherapy in comparison to no patients with TCA treated with more than 5 sessions. The positive periorbital AK was equal for both groups, while cheek, forehead, and nasal AK were close in both study groups with no significant difference. The temporal and scalp AK were also not significantly different in both study groups [Table 3].

Table 1: Distribution of actinic keratosis patient's demographic characteristics according to treatment types ($n=44$).

Variable	Cryotherapy (n=22) No. (%)	Trichloroacetic acid (n=22) No. (%)	P-value
Age (years)			
<50	3 (13.6)	8 (36.4)	0.1*
50–59	5 (22.7)	4 (18.2)	
60–69	8 (36.4)	3 (13.6)	
≥70	6 (27.3)	7 (31.8)	
Gender			
Male	11 (50.0)	7 (31.8)	0.2*
Female	11 (50.0)	15 (68.2)	
Occupation			
Indoor	20 (90.9)	22 (100.0)	0.1*
Outdoor	2 (9.1)	0 (0)	
Residence			
Urban	20 (90.9)	17 (77.3)	0.2*
Rural	2 (9.1)	5 (22.7)	

*Not significant

There was a significant association between good response to treatment and cryotherapy ($P = 0.02$); poor response was significantly higher among the patients treated with TCA (36.4%) in comparison to cryotherapy (4.5%). The post-treatment side effects between the study groups were not significantly different; redness was present in all the patients of both groups after treatment. Dyspigmentation was not significantly different between both study groups ($P = 0.1$); However, hyperpigmentation was higher in patients treated with TCA, while hypopigmentation was higher in the patients treated with cryotherapy [Table 4].

4. DISCUSSION

AK is regarded as one of the most common dermatological diseases globally (Berlin, 2010). The interesting characteristic of AK is their liability in development to squamous cell cancer. For that, early treatment of AK is preferred. Many destructive measures were used in the treatment of AK such as cryotherapy, TCA, curette, carbon dioxide, and erbium: YAG laser (Berlin, 2010). The present study showed a significant improvement of AK treated with cryotherapy in comparison to AK treated with TCA ($P = 0.02$). This finding is consistent with results of Lugo-Janer *et al.* which found that the cryotherapy is superior to TCA in the treatment of AK but the cryotherapy was painful and needs longer time (Lugo-Jan *et al.*, 2003).

The current study showed no significant differences between two study groups regarding side effects such as redness

Table 2: Distribution of actinic keratosis disease characteristics according to the treatment types ($n=44$)

Variable	Cryotherapy ($n=22$) No. (%)	Trichloroacetic acid ($n=22$) No. (%)	P-value
Duration of diseases (months)			
≤6	7 (31.8)	5 (22.7)	0.4*
>6	15 (68.2)	17 (77.3)	
Grade of lesion			
Mild	2 (9.1)	2 (9.1)	1.0*
Moderate	20 (90.9)	20 (90.9)	
Skin phototype			
Type II	4 (18.2)	0 (0)	0.1*
Type III	11 (50.0)	13 (59.1)	
Type IV	7 (31.8)	9 (40.9)	
Itching			
Yes	10 (45.5)	14 (63.6)	0.2*
No	12 (54.5)	8 (36.4)	
Skin cancer			
Yes	4 (18.2)	3 (13.6)	0.6*
No	18 (81.8)	19 (86.4)	
Previous occupation			0.002**
Indoor	13 (59.1)	3 (13.6)	
Outdoor	9 (40.9)	19 (86.4)	

*Not significant, **Significant

Table 3: Distribution of therapeutic characteristics for AK disease according to the treatment types ($n=44$)

Variable	Cryotherapy ($n=22$) No. (%)	Trichloroacetic acid ($n=22$) No. (%)	P-value
Number of sessions			
1	0 (0)	1 (4.5)	0.1*
2	2 (9.1)	4 (18.2)	
3	5 (22.7)	2 (9.1)	
4	6 (27.3)	3 (13.6)	
5	6 (27.3)	12 (54.6)	
>5	3 (13.6)	0 (0)	
Periorbital AK			
Yes	5 (22.7)	5 (22.7)	1.0*
No	17 (77.3)	17 (77.3)	
Cheek AK			
Yes	8 (36.4)	9 (40.9)	0.7*
No	14 (63.6)	13 (59.1)	
Forehead AK			
Yes	4 (18.2)	3 (13.6)	0.6*
No	18 (81.8)	19 (86.4)	
Nose AK			
Yes	12 (54.5)	14 (63.6)	0.5*
No	10 (45.5)	8 (36.4)	
Temporal AK			
Yes	6 (27.3)	2 (9.1)	0.1*
No	16 (72.7)	20 (90.9)	
Scalp AK			
Yes	1 (4.5)	2 (9.1)	0.1*
No	21 (95.5)	20 (90.9)	

*Not significant, AK: Actinic keratosis

and dyspigmentation. Although no significant difference, hypopigmentation was more among AK patients treated with cryotherapy. This finding is consistent with the results of other study (Vachiramom and Thadanipon, 2011). In our study, the outdoor occupation was significantly higher

among AK patients treated with TCA in comparison to patients treated with cryotherapy ($P = 0.002$). This finding may be attributed to many factors related to TCA such as easily application and cost that make it highly preferred by outdoor workers and dermatologists regardless of its efficacy

Table 4: Distribution of treatment response and side effects according to the treatment types (n=44)

Variable	Cryotherapy (n=22) No. (%)	Trichloroacetic acid (n=22) No. (%)	P-value
Response			
Good	16 (72.8)	9 (40.9)	0.02**
Moderate	5 (22.7)	5 (22.7)	
Poor	1 (4.5)	8 (36.4)	
Redness			
Yes	22 (100.0)	22 (100.0)	-
No	0 (0)	0 (0)	
Dyspigmentation			0.1*
No	6 (27.3)	6 (27.3)	
Hyperpigmentation	10 (45.5)	16 (68.2)	
Hypopigmentation	6 (27.3)	1 (4.5)	

*Not significant, **Significant; Good response=complete disappearance of the lesion; Moderate response=partial disappearance of the lesion; Poor response=lesion is still present regardless of size

or safety (Uhlenhake, 2013). The main study limitations were a short duration of the study which needs longer time for evaluation and assessment, in addition to the loss of some patients during follow-up period which was five patients in cryotherapy group and three patients in TCA group.

5. CONCLUSIONS

Cryotherapy is highly effective in treating the AK than TCA 25%. Further researches on effectiveness and safety of cryotherapy in treatment for AK are needed.

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