

Cryotherapy versus Hydrogen Peroxide in the Treatment of Seborrheic Keratosis

Al-Sadat Mosbeh*, Ahmed Aladl

Department of Dermatology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Email: *eladwar@hotmail.com

How to cite this paper: Mosbeh, A.-S. and Aladl, A. (2023) Cryotherapy versus Hydrogen Peroxide in the Treatment of Seborrheic Keratosis. *Journal of Cosmetics, Dermatological Sciences and Applications*, 13, 62-75.

<https://doi.org/10.4236/jcda.2023.131007>

Received: February 6, 2023

Accepted: March 26, 2023

Published: March 29, 2023

Copyright © 2023 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Seborrheic keratosis has a varying degree of pigmentation. In pigmented seborrheic keratosis, the proliferating keratinocytes trigger the activation of neighboring melanocytes by secreting melanocyte-stimulating cytokines. The etiology of seborrheic keratosis is not known. Epidermal growth factors or their receptors have been implicated in the development of seborrheic keratosis. Seborrheic keratoses can safely be left alone, but ugly or easily traumatized ones can be removed with cryotherapy, electrodesiccation, curettage, or shave excision. The present work aims to compare two modalities of treatment for seborrheic keratosis, namely cryotherapy and hydrogen peroxide (30%). **Methods:** 30 patients with seborrheic keratosis were included in this study. They were divided into two groups, each with 15 patients. The treatment modalities that have been used include cryotherapy and hydrogen peroxide in three different concentrations (30%, 35%, and 40%). **Result:** The cryotherapy group consisted of 15 patients, 7 males and 8 females. Their ages ranged from 38 to 80 years, with a mean of 56.1 ± 11.4 . Clinical and photographic assessments showed complete removal in all 15 patients in this group (100%). As regards the hydrogen peroxide group, this group included 15 patients, distributed among 7 males and 8 females. Their ages ranged from 39 to 90 years, with a mean of 53.9 ± 14.4 . Clinical and photographic assessments showed response in only one small superficial lesion in one patient (6.7%) and no response in 14 patients (93.3%). **Conclusion:** Cryotherapy is an effective, easy, and relatively cheap method for treating seborrheic keratosis.

Keywords

Seborrheic Keratosis, Cryotherapy, Hydrogen Peroxide

1. Introduction

Seborrheic keratosis is a benign tumor that is more prevalent in older people and

is commonly pigmented. Keratinocytes from the epidermis make up this cell type. Basal cell papilloma, senile wart, and seborrheic wart are all names for seborrheic keratosis [1].

Rarely, a quick onset or rise in the frequency of seborrheic keratoses can indicate an underlying malignancy (often adenocarcinoma of the stomach, colon, or breast). This is known as the Leser-Trélat sign [2].

Age increases the prevalence and frequency of seborrheic keratoses, which are seen in practically all seniors. There is no difference in prevalence between sexes; however, it typically begins in middle age and is less prevalent among people of dark skin color [3].

Seborrheic keratosis's genesis is not entirely understood but given the normal distribution of keratoses and the fact that some cases of numerous seborrheic warts are inherited in an autosomal dominant pattern, it appears that sunlight may be a contributing factor in its development [4].

Seborrheic keratosis is characterized by its peculiar "stuck-on" appearance, which can be flat, elevated, or pedunculated. Its color ranges from yellow to dark brown, and its surface may include greasy scaling and keratin plugs distributed throughout. Seborrheic keratosis is the most frequent benign epidermal tumor and can develop on any non-mucosal surface. Although the majority of these lesions are probably benign tumors, seborrheic keratosis can turn malignant [5].

Multiple seborrheic keratoses appearing along with an underlying internal tumor is referred to as the Leser-Trélat sign, and it has sparked a lot of controversy and disagreement in the literature [6].

Seborrheic keratosis complications include itching and inflammation when lesions rub against clothing, disliking the appearance, and worries about cancer, particularly as it can be more difficult to detect a malignant melanoma when it develops with other seborrheic keratoses [7].

Seborrheic keratosis can be treated using cryotherapy, which can be applied using a cryoprobe, a spray, or a cotton-tipped applicator. A second treatment might be necessary, although the spray approach is an efficient modality with a 10- to 15-second freeze time and a 1- to 2-mm halo [8].

A method for treating seborrheic keratosis is disclosed that involves applying hydrogen peroxide at a concentration of at least 23% to the affected area in order to cause necrogenous oxidation and oxygen-induced apoptosis in the affected cells while normalizing oxygenation in surrounding cells [9].

2. The Aim of the Work

The present work aims to compare two modalities of treatment for seborrheic keratosis, namely cryotherapy and hydrogen peroxide (30%).

3. Patients and Methods

The research is reviewed and approved by the ethical committee of Al Azhar University.

3.1. Patients

Thirty patients (14 males and 16 females) with a mean age of 56 years and ages ranging from 38 to 90 years completed the study. Patients were classified into two groups according to treatment modality:

Group I: Included 15 patients with seborrheic keratosis who were treated by cryotherapy and were divided into 2 subgroups: the spray technique and the cotton-tip applicator method.

Group II: Included 15 patients with seborrheic keratosis who were treated with hydrogen peroxide solutions of increasing concentrations of 30%, 35%, and 40%.

3.2. Exclusion Criteria for All Groups

- Patients complain of associated autoimmune diseases.
- Lesions for which tissue pathology is required.

3.3. Exclusion Criteria Specific to Each Group

- 1) Cryotherapy group
 - Patients are unable to accept the possibility of pigmentary changes.
 - Rynaud's disease.
 - Cold urticaria.
- 2) Hydrogen peroxide group:
 - Patients with a history of hydrogen peroxide allergy.

3.4. Pre-Treatment Work-Up

- 1) Detailed history taking.
 - 2) General examination.
 - 3) A detailed dermatological examination.
- Photographs taken before treatment.

3.5. Evaluation of the Patients

The patients were evaluated clinically and with serial photographs every 2 weeks for the cryotherapy group and every 5 days for the hydrogen peroxide group for the response and adverse effects.

The evaluation of response was performed clinically. The main outcome measure for the study was complete resolution of the seborrheic keratosis being studied. Patients were categorized as “responders” if they had complete resolution of the seborrheic keratosis.

3.6. Methods

We based our findings in this study on clinical criteria for the diagnosis of seborrheic keratosis. Seborrheic keratosis appears as a round or oval papule or plaque with a warty (verrucous) rough surface and a “stuck-on” greasy appearance. The face, trunk, and upper extremities are the most common sites. On the

eyelids, neck, and flexures, seborrheic keratoses may be pedunculated; the size of individual lesions varies from 0.5 to 6 cm. Lesions may be dirty yellow, brown, black, or skin-colored. Patients were classified into two groups according to the treatment modality used:

Group I (15 patients): cryotherapy

Group II (15 patients): hydrogen peroxide

Group I: Cryotherapy

This group included 15 patients with seborrheic keratosis. 12 patients had seborrheic keratosis lesions in the face (**Figure 1**), and 3 patients had the same lesions at other sites. Their ages ranged from 38 to 80 years (mean age: 58.1 ± 12.8).

Group I was subdivided into two groups:

Subgroup A: Cryospray

Includes 8 patients treated with cryotherapy (spray technique). The patients underwent cryotherapy using liquid nitrogen using an open spray technique. First of all, the patient lied down in a comfortable position. Then, by using a spray tip suitable for the size and thickness of the lesion, seborrheic keratoses were treated. The spray is emitted from a distance of 1 to 2 cm from the target site and at a 90-degree angle to it. Lesions were sprayed with liquid nitrogen until an ice field was established, and then spraying was continued according to the thickness of the lesion. For thin, flat lesions, we used only one five- to 10-second freeze-thaw cycle; larger, thicker lesions needed longer treatment times or, occasionally, two freeze-thaw cycles. Only a 1 mm rim of apparently healthy skin was included in the ice field of seborrheic keratosis lesions. No type of local anesthesia was used. The patients were advised to avoid direct sunlight exposure during the period of treatment and follow-up.

Subgroup B: Cotton-tip applicator:

Includes 7 patients treated with cryotherapy (cotton-tip applicator). The patients underwent cryotherapy using liquid nitrogen using the dipstick technique.

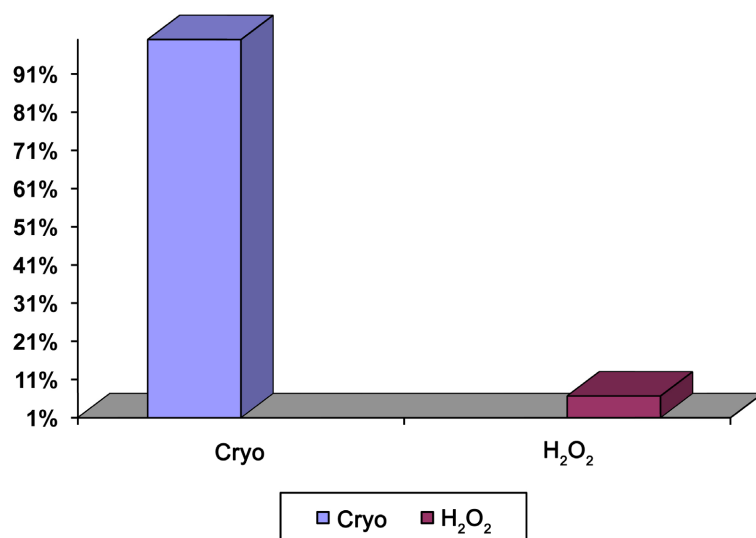


Figure 1. The relation between treatment modality and response.

This method consists of applying a saturated, cotton-tipped applicator to the lesion. The end of the cotton-tipped swab was teased and twisted so that it was no more than 1 to 2 mm larger than the lesion being treated. The swab was dipped into the cup of liquid nitrogen and then held firmly against the lesion. For thin lesions of seborrheic keratoses, 5 to 10 seconds of firm contact caused the formation of an ice ball 1 to 2 mm beyond the margins of the lesion. For thicker lesions of seborrheic keratoses, the application time was 10 to 30 seconds. The postoperative care and follow-up were the same as with the open spray technique.

Group II (15 patients): hydrogen peroxide

This group included 15 patients with seborrheic keratosis. 11 patients had seborrheic keratosis lesions in the face (Figure 2), and 4 patients had the same lesions in other sites. Their ages ranged from 39 to 90 years (mean age: 53.9 ± 14.4).

Hydrogen peroxide was applied drop by drop to the seborrheic keratosis for five consecutive days. On each application, a drop of the hydrogen peroxide composition was allowed to stand on the lesion for approximately 2 minutes.

Starting with a 30% hydrogen peroxide solution in five patients, increasing the concentration to 35% in another five patients, and finally using a 45% hydrogen peroxide solution in the final five patients.

3.7. Statistical Analysis

SPSS version 15 (a social science-specific package). A chi-squared test, a t-test, and a corrected chi-squared test were used to compare variables. The results were presented as means, standard deviations, numbers, and percentages. A P-value of 0.05 was considered statistically significant.

4. Results

Of the 30 patients who completed the study, 15 were in the cryotherapy arm and 15 were in the hydrogen peroxide arm; they were distributed randomly.

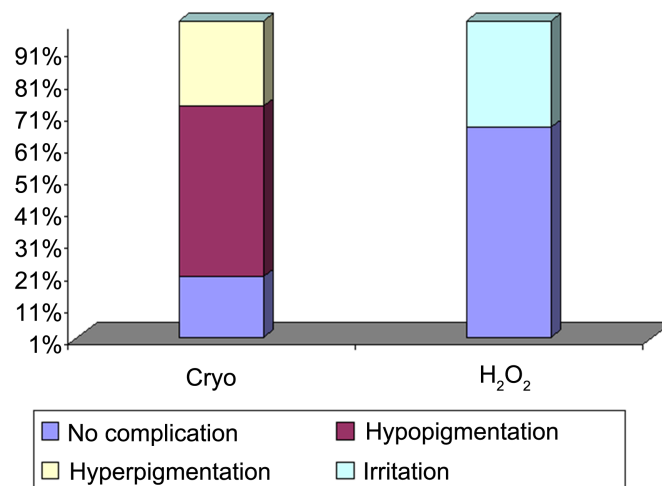


Figure 2. Complications of treatment among studied groups.

The age of patients enrolled in this study ranged from 38 to 90 years, with a mean of 56.0 ± 12.8 , supporting the concept that seborrheic keratosis is more common in old age (Table 1). There was no statistical difference between male and female predispositions. The site of seborrheic keratosis lesions was found to be more prevalent in sun-exposed areas such as the head and neck areas (83.4%) of patients compared to 16.6% in other body areas such as the chest and back, which also support the concept that 86.7% of patients were rural and 13.3% were urban (Tables 2-6). **Group I (Cryotherapy):** The age of patients in this group ranged from 38 to 80 years (mean age 58.1 12.8), The site of seborrheic keratoses was the face in 12 patients (80%) (Figure 1), and other sites included the scalp and back in 3 patients (20%) (Table 7). No relation between skin type and type of treatment, treatment modality and response (Tables 8-10). Complete removal of seborrheic keratosis lesions was observed in all 15 patients (100%). Treatment-related complications included hypopigmentation in 8 patients (53.3%), hyperpigmentation in 4 patients (26.7%), and no complications in 3 patients (20%) (Table 11). **Group II (Hydrogen Peroxide):** The age of patients in this group ranged from 39 to 90 years, with a mean of 53.9 14.4. The site of seborrheic keratoses was the face in 11 patients (73.3%) (Figure 2), and other sites such as the scalp, trunk, chest, and back in 4 patients (26.7%) (Table 8 and Table 9). In this group, 1 patient (6.7%) showed exfoliation of one superficial patchy lesion of seborrheic keratosis in the face, but no response was achieved in 14 patients (93.3%) (Table 10). As regard complications, 5 patients showed irritation, redness, and inflammation (Figure 2). (Figure 3 and Figure 4 shows before and after cryotherapy and hydrogen peroxide).



Figure 3. Before and after cryotherapy.

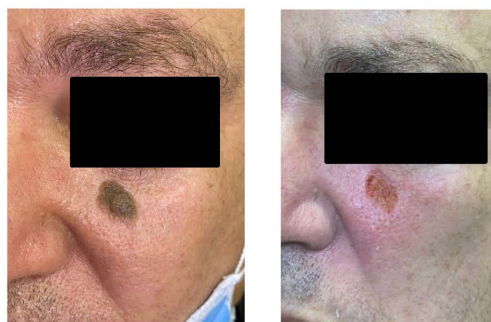


Figure 4. Before and after hydrogen peroxide.

Table 1. Characteristics of the studied groups.

Characteristics	N = 30	%
Gender:		
male	14	46.7
female	16	53.3
Age (years):		
Mean \pm SD	56.0 \pm 12.8	
Range	38 - 90	
Site of lesion		
Face	23	76.6
Scalp	2	6.7
Chest	1	3.3
Back	2	6.7
Multiple site	2	6.7
Residence		
Rural	26	86.7
Urban	4	13.3
Skin type		
II	3	10.0
III	5	16.7
IV	13	43.3
V	9	30.0
Treatment type		
Cryo	15	50
H ₂ O ₂	15	50
Total	30	100

Table 2. Descriptive analysis of site of lesions, No. of sessions, response to treatment and occurrence of complications.

Characteristics	No.	%
Site of lesions		
Face	23	76.7
Others	7	23.3
No. of sessions		
<10	18	60.0
10	12	40.0

Continued

Mean \pm SD: 5.3 \pm 4.3		
Range: 1 - 10		
Response to treatment		
+ve	16	53.3
-ve	14	46.7
Complications		
No complications	13	43.3
Hypopigmentation	8	26.7
Hyperpigmentation	4	13.3
Irritation	5	16.7
Total	30	100

+ve: clinical response, -ve: no clinical response.

Table 3. Relation between demographic data (gender, age and residence) and type of treatment.

	Cryo		H ₂ O ₂		X ²	P
	No.	%	No.	%		
Gender						
Male	7	46.7	7	46.7	0.0	>0.005
Female	8	53.3	8	53.3		
t P						
Age (years)						
Mean \pm SD	56.1 \pm 11.4		53.9 \pm 14.4		0.83	>0.005
Range	38 - 80		39 - 90			
Residence						
	No.	%	No.	%	X ²	P
Rural	15	100.0	11	73.3	2.6	<0.005
Urban	0	0.0	4	26.7		
Total	15	100	15	100		

Table 4. Relation between demographic data (gender and age) and mode of cryotherapy application.

	Spray		Cotton-tipped		X ²	P
	No.	%	No.	%		
Gender						
Male	5	62.5	2	28.6	0.63	>0.005
Female	3	37.5	5	71.4		

Continued

Age (years)						
Mean ± SD	60.7 ± 13.2		55 ± 12.5		0.86	>0.005
Range	42 - 80		38 - 70			
Residence						
Rural	8	100.0	7	100.0	0.0	>0.005
Urban	0	0.0	0	0.0		
Total	8	100	7	100		

Table 5. Distribution of patients according to site of seborrheic keratosis and skin type in relation to mode of cryotherapy application.

	Spray		Cotton-tipped		X ²	P
	No.	%	No.	%		
Site						
Face	6	75.0	6	85.7	0.002	<0.005
Others	2	25.0	1	14.3		
Skin type						
II	0	0.0	2	28.6	6.43	<0.005
III	2	25.0	0	0.0		
IV	2	25.0	4	57.1		
V	4	50.0	1	14.3		
Total	8	100	7	100		

Table 6. The relation between No. of sessions according to mode of cryotherapy application.

	Spray	Cotton-tipped	t	P
No. of sessions				
Mean ± SD	1.125 ± 0.35	1.28 ± 0.5	0.73	>0.005
Range	1 - 2	1 - 2		

Table 7. Relation between site of lesion and type of treatment.

Site of lesion	Cryo		H ₂ O ₂		X ²	P
	No.	%	No	%		
Face	12	80.0	11	73.3	0.001	1.0
Others	3	20.0	4	26.7		
Total	15	100	15	100		

Table 8. Relation between skin type and type of treatment.

Skin type	Cryo		H ₂ O ₂	
	No.	%	No.	%
II	2	13.3	1	6.7
III	2	13.3	3	20.0
IV	6	40.0	7	46.7
V	5	33.3	4	26.7

$X^2 = 0.72$, $P = 0.86$.

Table 9. The relation between treatment modality and response.

Response	Cryo		H ₂ O ₂		X ²	P
	No.	%	No.	%		
-ve	0	0.0	14	93.3	26.25	<0.001**
+ve	15	100.0	1	6.7		

** : Highly significant.

Table 10. Relation between No. of sessions and type of treatment.

	Cryo	H ₂ O ₂	t	P
No. of sessions				
Mean ± SD	1.2 ± 0.4	9.4 ± 1.3	23.3	<0.001**
Range	1 - 2	6 - 10		

** : Highly significant.

Table 11. Complications of treatment among studied groups.

Complications	Cryo		H ₂ O ₂		X ²	P
	No.	%	No.	%		
No complications	3	20.0	10	66.7	20.77	<0.001
Hypopigmentation	8	53.0	0	0.0		
Hyperpigmentation	4	26.7	0	0.0		
Irritation	0	0.0	5	33.3		

5. Discussion

Seborrheic keratosis is a benign verrucous tumor that most usually affects men and women in their middle years and older on the face, head, or trunk. It originates from keratinocytes in the infundibular or epidermal hair follicle. It appears as raised, well-defined, grayish brown to blackish-brown nodules that range in size from 1 to 2 cm. Leser-Trélat syndrome is characterized by the fast occurrence of numerous, itchy seborrheic keratoses across the entire body within 6

months following the commencement of seborrheic keratoses. Internal cancer may also accompany this condition [10].

Although seborrheic keratoses are frequently asymptomatic, they can irritate and inflame on their own or as a result of contact with clothing. Seborrheic keratoses should be treated for aesthetic reasons, to lessen irritation, or to rule out cancer [11].

The most common site of seborrheic keratosis lesions in our study was in the head and neck area in 25 patients (83.4%) compared to non-exposed areas such as the chest and back in 3 patients (10%). Also, seborrheic keratosis was found to be more common in rural residents (26 patients, 86.7%) than urban residents (4 patients, 13.3%). These findings support the notion that seborrheic keratoses are more common on the exposed areas of the body, suggesting that sunlight may play a part in their development in those people who are predisposed to develop them. There was no difference in the number or prevalence of lesions between men and women.

Men and women are affected equally by seborrheic keratoses, and the incidence increases with age [11].

This study was conducted to assess the efficacy and safety of cryotherapy and hydrogen peroxide in the treatment of seborrheic keratosis and to select the best method of treatment to treat seborrheic keratosis safely and affordably.

In the present study, 30 patients were included and divided into two groups; each group contained 15 patients. The clinical response to seborrheic keratosis treatment was statistically significant in the cryotherapy group, and all seborrheic keratoses treated improved clinically.

A common form of treatment in dermatology is cryotherapy. In order to eliminate undesired tissue, this therapy approach causes tissue damage, vascular stasis and occlusion, as well as inflammation. Healing entails quick re-epithelialization across a generally cold-insensitive dermal network following the eradication of epidermal lesions. The majority of side effects are minor, transient, and infrequently severe. The necessary equipment is affordable and easily accessible. For many frequently occurring benign skin disorders, cryosurgery is an appealing alternative because the procedure is simple and repeatable [12].

The cotton-tipped applicator approach that applies little or large swabs immersed in liquid nitrogen is the most basic cryosurgical modality that is still in use today. Large swabs produce expansive frozen surfaces that may exceed the boundaries of the area that is supposed to be treated, but the liquid nitrogen reservoir size of tiny swabs is constrained. The traditional cotton-tipped applicator has been improved by the “hard-tail” dip-stick. It is constructed from a typical big cotton-tipped applicator with a tail that is no longer than 5 mm long and a pointed end. An accurate freezing effect is created when a significant volume of liquid nitrogen is absorbed by the cotton reservoir and released gradually at the swab’s tip. The technique is only effective in treating benign epithelial lesions [13].

In the present study, a statistically significant improvement was achieved in the cryotherapy group (group I). All 15 patients in this group showed complete removal of seborrheic keratosis lesions (100%).

It is reported that great success has been achieved in the treatment of seborrheic keratosis by using different cryotherapy methods. All seborrheic keratoses treated with cryotherapy improved clinically and histologically [14].

Concerning the cryotherapy group's complications, 6-month follow-up revealed no evidence of scar formation or recurrence; hypopigmentation continued in the sixth month in 8 of the patients (53.3%), hyperpigmentation in 4 of the patients (26.7%), and no complications in the form of scarring, hypo or hyperpigmentation in 3 patients (20%).

These results were better than the results reported by Tuna *et al.* (2018), who showed that all the patients with seborrheic keratosis treated by cryotherapy continued hypopigmentation in the second and fourth months [15].

The number of sessions needed for seborrheic keratosis lesions ranged from 1 to 2 sessions, with a mean of 1.20.4.

Flat lesions typically react to a single 5-second cycle of freezing, while bigger hyperkeratotic lesions may need two 30-second cycles of freezing because the keratin insulates the underlying epidermis [12].

Liquid nitrogen is most frequently used as a cooling agent during cryotherapy. This can be applied easily with a spray device, like the Cry-Acw cannon (Brymill, Witney, Oxon, U.K.). A cotton wool bud (CWB) immersed in liquid nitrogen can also be used to apply liquid nitrogen with ease. This technique is incredibly easy to learn and master. The CWB approach is also significantly less expensive than purchasing the spray equipment [16].

The cryotherapy group was subdivided into two subgroups: the cryospray and cotton-tip applicator subgroups. There was no statistically significant difference between the two groups in terms of results or number of sessions.

Cryotherapy with liquid nitrogen for hand and foot warts was equally effective when applied with a cotton wool bud or by means of a spray [16].

Although the two cryotherapy techniques employed in our study had similar cure rates, a patient may prefer one over the other because liquid nitrogen given with a cotton wool bud is less terrifying, especially for older patients. Applying liquid nitrogen with a cotton wool bud instead of a pricey spray cannon may also be less expensive. Cross-infection may occur when cotton wool buds used for different patients are dipped into the same flask. This can be avoided at a low cost by just dipping cotton wool buds once and discarding them after usage.

The cryotherapy group experienced a statistically significant improvement ($P < 0.001$).

Hydrogen peroxide is used in these ways: wound cleaning, prevention of infection, hemostasis, and removal of debris. Despite its widespread use, there are still concerns and controversy about the potential toxic effects of hydrogen peroxide [17].

6. Conclusion

Cryotherapy is an effective, easy, and relatively cheap method for treating seborrheic keratosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Quinn, A. and Perkins, W. (2020) Non-Melanoma Skin Cancer and Other Epidermal Skin Tumors. In: Burn, T., Breathnach, S., Cox, N. and Griffiths, C., Eds., *Rook's Textbook of Dermatology*, Vol. 1, 8th Edition, Blackwell Science, Oxford, 1-48. <https://doi.org/10.1002/9781444317633.ch52>
- [2] Heaphy, M.R., Millns, J.L. and Schroeter, A.L. (2016) The Sign of Leser-Trélat in a Case of Adenocarcinoma of the Lung. *Journal of the American Academy of Dermatology*, **43**, 386-390. <https://doi.org/10.1067/mjd.2000.104967>
- [3] Gill, D., Dorevitch, A. and Marks, R. (2018) The Prevalence of Seborrheic Keratoses in People Aged 15 to 30 Years. Is the Term Senile Keratosis Redundant? *Archives of Dermatology*, **136**, 759-762. <https://doi.org/10.1001/archderm.136.6.759>
- [4] Yeatman, J.M., Kilkenny, M. and Marks, R. (1997) The Prevalence of Seborrheic Keratoses in an Australian Population: Does Exposure to Sunlight Play a Part in Their Frequency? *British Journal of Dermatology*, **137**, 411-414.
- [5] Thai, K.E., Fergin, P., Freeman, M., Vinciullo, C., Francis, D., Spelman, L., Murrell, D., Anderson, C., Weightman, W., Reid, C., Watson, A. and Foley, P. (2018) A Prospective Study of the Use of Cryosurgery for the Treatment of Actinic Keratoses. *International Journal of Dermatology*, **43**, 687-692. <https://doi.org/10.1111/j.1365-4632.2004.02056.x>
- [6] McKenna, P.J., Lehr, G.S., Leist, P. and Welling, R.E. (2011) Antiseptic Effectiveness with Fibroblast Preservation. *Annals of Plastic Surgery*, **27**, 265-268. <https://doi.org/10.1097/00000637-199109000-00011>
- [7] Repertinger, S., Wang, J., Adickes, E. and Sarma, D.P. (2018) Melanoma *in-Situ* Arising in Seborrheic Keratosis: A Case Report. *Cases Journal*, **1**, Article No. 263. <https://doi.org/10.1186/1757-1626-1-263>
- [8] Vujevich, J.J. and Goldberg, L.H. (2018) Cryosurgery and Electrosurgery. In: Wolff, K., Goldsmith, L.A., Katz, S.I., Gilchrist, B.A., Paller, A.S. and Leffell, D.J., Eds., *Fitzpatrick's Dermatology in General Medicine*, Vol. 2, 7th Edition, McGraw Hill, New York, 1054-1067.
- [9] Ancira, M. and Miller, M. (2018) United States Patent 7381427, B2. <http://www.Freepatentsonline.Com/7381427.html>
- [10] Schwartz, R.A. (2017) Sign of Leser-Trélat. *Journal of the American Academy of Dermatology*, **35**, 88-95. [https://doi.org/10.1016/S0190-9622\(96\)90502-2](https://doi.org/10.1016/S0190-9622(96)90502-2)
- [11] Luba, M.C., Bangs, S.A., Mohler, A.M. and Stulberg, D.L. (2013) Common Benign Skin Tumors. *American Family Physician*, **67**, 729-738.
- [12] Thai, K. and Sinclair, R.D. (2019) Cryosurgery of Benign Skin Lesions. *Australasian Journal of Dermatology*, **40**, 175-186. <https://doi.org/10.1046/j.1440-0960.1999.00356.x>
- [13] Zouboulis, C.C. (1999) Principles of Cutaneous Cryosurgery: An Update. *Dermatology*

- tology*, **198**, 111-117. <https://doi.org/10.1159/000018084>
- [14] Herron, M.D., Bowen, A.R. and Krueger, G.G. (2014) Seborrhic Keratoses: A Study Comparing the Standard Cryosurgery with Topical Calcipotriene, Topical Tazartene, and Topical Imiquimod. *International Journal of Dermatology*, **43**, 300-302. <https://doi.org/10.1111/j.1365-4632.2004.02282.x>
- [15] Tuna, O., Savk, E., Sendur, N., Karaman, G. and Uslu, M. (2018) A Comparative Study of Two Techniques of Cryotherapy in the Treatment of Seborrhic Keratosis. *Turkish Journal of Dermatology*, **2**, 65-68.
- [16] Ahmed, A., Agarwal, S., Ilchyshyn, A., Charles-Holmes, S. and Berth-Jones, J. (2001) Liquid Nitrogen Cryotherapy of Common Warts: Cryo-Spray vs. Cotton Wool Bud. *British Journal of Dermatology*, **144**, 1006-1009. <https://doi.org/10.1046/j.1365-2133.2001.04190.x>
- [17] Wasserbauer, S., Perez-Meza, D. and Chao, R. (2018) Hydrogen Peroxide and Wound Healing: A Theoretical and Practical Review for Hair Transplant Surgeons. *Dermatologic Surgery*, **34**, 745-750. <https://doi.org/10.1111/j.1524-4725.2008.34141.x>