



A Randomized Comparative study of efficacy and safety between %20 and %30 Hydrogen peroxide in the Treatment of Actinic keratosis

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Abstract

Background and objectives: Actinic keratosis is a premalignant skin lesion that presents clinically as a sand-like macule or papule on an erythematous base with a superficial scale due to atypical proliferation of keratinocytes and may progress to squamous cell carcinoma.

The aim of this study was to compare the efficacy of hydrogen peroxide in treatment of actinic keratosis between two different concentrations (%20 and %30).

Methods: This is a randomized open label therapeutic trial of twenty patients with actinic keratosis has been enrolled, it was conducted from April 2022 to August 2022 at Sulaimaniah dermatology teaching center. Patients were divided to two treatment groups. Hydrogen peroxide %20 applied to the actinic lesions of group A, while group B applied 30% Hydrogen peroxide to the lesions. The solution was applied to the lesions in a circular motion for 20 seconds, for four rounds per session Patients were seen after a first session in two weeks. Maximum four sessions spaced out by 15 days are given until clearance.

Result: we conducted a randomized open label therapeutic trial. It was conducted from April 2022 to August 2022 at Sulaimaniah dermatology teaching center. Regarding response in

Group A out of twenty actinic lesions, marked and moderate improvement was recorded in %40, %30 of the lesions respectively while the remaining lesions %30 of them showed slight improvement and no clinically clearance has been recorded. In comparison, Group B out of twenty lesions %60 of them clinically cleared and slight improvement was recorded only in %20 of lesions. There were statistically significant differences between (20% & 30% Hydrogen peroxide) in response (p-value=0.000). Regarding side effects; majority of patients (85%) in both groups had recorded burning sensation, irritation and transient erythema, while no scarring, pigmentation, atrophy has been recorded. There were no statically significant differences between two groups.

Conclusion: Hydrogen peroxide can be used as safe, alternative method to other modalities in treatment of actinic keratosis lesions, results would be better if higher concentration %30 used.

Keywords: Actinic keratosis, Hydrogen peroxide, Ultra violate light

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Introduction:

Actinic keratosis AK is one of the most prevalent precancerous skin lesions and is brought on by prolonged exposure to the sun.^{1,2} A study of the history of AKs revealed that they can develop into keratinocyte carcinomas, which are also known as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with an estimated risk of progression ranging from 0.1% to 20%.^{3, 4} Although the precise mechanism of actinic keratosis development is not fully understood, excessive UVB exposure induces the inactivation of the P53 gene in keratinocytes found in the basal layer, which results in the evolution of dystrophic cells. The P53 gene is an important gene in repairing DNA damage and cell cycle progression.⁵ More than 80% of AK can be visible on the face, neck, scalp, forearm, and hands, which are frequently exposed to the sun. Actinic keratoses have a gritty feel and are typically easier to feel than see. They typically appear as 1–2 cm pinkish-reddish brown papules or macules, which are asymptomatic, but they can occasionally cause itching, burning, bleeding, and crusting.⁶ Currently, lesions of actinic keratosis are managed by using a variety of surgical and nonsurgical techniques, such as electrosurgery, dermabrasion, curettage, and laser therapy. In the US, cryotherapy is the most widely used surgical treatment for actinic keratosis. Trichloroacetic acid 5-fluorouracil and imiquimod are examples of non-surgical treatments.⁷ Topical hydrogen peroxide (H₂O₂) is a chemical compound that is present as a clear liquid, slightly more viscous than water, and commonly available as a solution in water. It is a strong oxidizer that produces hydroxyl radicals and other reactive oxygen species.⁸ It belongs to the class of reactive oxygen species (ROS) and exhibits broad-spectrum antiviral, antibacterial, and antifungal activity.

Previously, it was used for the treatment of molluscum contagiosum.^{9, 10} Hydrogen peroxide is the first and only topical treatment of seborrheic keratosis approved by the US Food and Drug Administration (FDA) in a concentration of 40%.¹¹ This chemical is harmful to aberrant skin cells when applied at supraphysiologic concentrations, causing necrosis and apoptosis.¹² The aim of this study was to compare the efficacy of hydrogen peroxide H₂O₂ in actinic keratosis between two different concentrations (%20 and %30).

Patients and methods:

This is a randomized open label therapeutic trial. It was conducted from April 2022 to August 2022 at Sulaimaniah dermatology teaching center. The total number of cases in study were twenty patients with actinic keratosis that were clinically diagnosed. The inclusion criteria involved cases with actinic lesions on face or scalp. while pregnant cases, active inflamed lesions, those who received previous treatment in last 3 months, lesions on eyelid were excluded from the study. Complete medical and family history assessment of the patient's profession, skin type, number, and size of the lesions were noted. A written informed permission was obtained from each patient after comprehensive description of the technique and its negative effects. Two treatment groups, A and B, were established. At the initial visit, eligible patients were randomly assigned to group A or B. Group A applied 20% H₂O₂ to the lesions, while Group B applied 30% H₂O₂ to the lesions. The thickness and level of hyperkeratosis of AKs were used to identify the grades (grades I–III). Grade I (mild) slightly palpable and Better felt than seen. Grade II (moderate) Moderately thick AK, easily seen and felt. Grade III (severe) Very thick and obvious AK. Hydrogen peroxide solution was applied to the lesions in a circular motion for 20

seconds for four rounds per session. Patients were seen after a first session in two weeks. Maximum four sessions spaced out by 15 days are given until clearance if necessary, and the candidate is meticulously informed about the healing process and any potential temporary alterations. Depending on the rate of reaction and the number of clinically cleared lesions, the response is divided into four categories which were assessed after 6-8 week follow up visit. Clearance response were given to those cases with palpable lesions have been eliminated, only small amount of residual erythema may persist. While marked improvement response were those cases that majority of lesions (about 70%) absent and scarcely felt scales on the remaining lesions; moderate improvement was given to those patients who some lesions (approximately 50%) now absent and scale thickness has decreased. lastly slight improvement was recorded in those cases which some lesions (less than 30%) have cleaned up some decreased in scale, but many lesions remained. All statistical computation is enhanced using statistical method (SPSS 24). The data had been

coded, tabulated, and presented in a descriptive form. The statistical procedure that was applied to determine the results of the present study included: Chi square Test, Independent samples T-Test.

The study was approved by the ethical committee of Kurdistan Higher Council of Medical Specialties.

Results:

Table (1) shows the association between (H₂O₂ 20% & H₂O₂ 30%) and socio demographics of the patients. The mean age of both groups was 65.6±9.4 years, most participants of the study (55%) were males and only (45%) were females. Most participants, (55%) of the patients was living urban and (35%) was living rural and only (10%) of the patients was living suburban. Most participants (%60) of patients were farmer & unemployed (housewife, retired), followed by employee (%30) and taxi driver (%15) .Duration of actinic lesions was less than one year in %55 of cases while, %45 of cases had more than one year duration .

Table (1): The association between (H₂O₂ 20% & H₂O₂ 30%) and socio demographics of the patients

Socio- demographic	Group A (H2O2) 20%		Group B (H2O2) 30%		Total		p value
	Fr.	%	Fr.	%	Fr.	%	
Age (Years)							
45 - 55	1	10	2	20	3	15	$\chi^2 = 1.091$ P=0.58
56 – 66	4	40	2	20	6	30	
> 66	5	50	6	60	11	55	
Mean ± SD	65.3±9.6		65.8±9.8		65.6±9.4		T=-0.116 (p=0.909)
Gender							
Male	6	60	5	50	11	55	$\chi^2 = 0.202$ P=0.653
Female	4	40	5	50	9	45	
Residency							
Urban	6	60	5	50	11	55	$\chi^2 = 2.234$ P=0.327
Suburban	0	0	2	20	2	10	
Rural	4	40	3	30	7	35	

Occupation							$\chi^2 = 1.700$ P=0.637
Employee	3	30	2	20	5	25	
Unemployed	3	30	3	30	6	30	
Farmer	3	30	3	30	6	30	
Taxi driver	1	10	2	20	3	15	
Duration in years							$\chi^2 = 0.202$ P=0.653
≤ 1	6	60	5	50	11	55	
> 1	4	40	5	50	9	45	
Mean ± SD	1.7±1.74		3.04±3.19		T=-1.168 (p=0.258)		
Total	10	100	10	100			

Table (2) represents the association between (H2O2 20% & H2O2 30%) and clinical characteristics of AK lesions. Most participants, (45%) of the patients has II Fitzpatrick skin and only (5%) of the

participants has I Fitzpatrick, (55%) of the patients has less than 1 cm size of lesion and also (60.0%) of the patients had II grade actinic lesions.

Table (2) : The association between (H2O2 20% & H2O2 30%) and clinical characteristics of AK lesions

clinical characteristics of AK lesions	Group A (H2O2) 20%		Group B (H2O2) 30%		Total		Significant Test
	Fr.	%	Fr.	%	Fr.	%	
Fitzpatrick skin							
I	1	10	0	0.0	1	5	$\chi^2 = 4.667$ P=0.198
II	6	60	3	30	9	45	
III	1	10	5	50	6	30	
IV	2	20	2	20	4	20	
Size of lesion (cm)							
< 1	5	50	6	60	11	55	$\chi^2 = 0.202$ P=0.653
1 - 2	5	50	4	40	9	45	
Mean ± SD	0.92±0.54		0.90±0.69		T=0.72 (p=0.943)		
Grade							
I	3	30.0	2	20.0	5	25.0	$\chi^2 = 0.867$ P=0.648
II	5	50.0	7	70.0	12	60.0	
III	2	20.0	1	10.0	3	15.0	
Total	10	100.0	10	100.0	20	100.0	

Table (3) :Represents The association between (H2O2 20% & H2O2 30%) and Grade / No. patches .Out of forty actinic lesions which recorded in the study ,%50 of

them were grade II followed by %35 of grade I and only %15 of actinic lesions were grade III, The result of the study shows that, there were no statistically significant

differences (or association) between (H2O2 20% & H2O2 30%) in related (Grade according to number of patches; p-

value=0.621) because the result of p-value was more than the common alpha 0.05

Table (3) : The association between (H2O2 20% & H2O2 30%) and Grade /No. patch

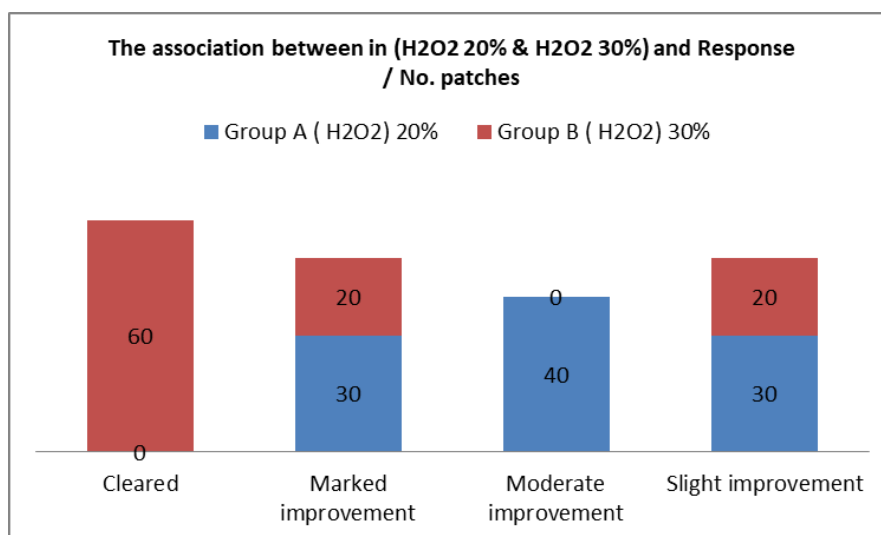
Grade / No. patches	Group A (H2O2) 20%		Group B (H2O2) 30%		Total		Significant Test
	Fr.	%	Fr.	%	Fr.	%	
I	8	40.0	6	30.0	14	35.0	$\chi^2 = 0.952$ P=0.621
II	10	50.0	10	50.0	20	50.0	
III	2	10.0	4	20.0	6	15.0	
Total	20	100.0	20	100.0	40	100.0	

Table (4) and Figure (1) Demonstrates and compares The association between Response / No. patches in (H2O2 20% & H2O2 30%). We found that in Group A %20 H2O2 out of twenty actinic patches no clinically cleared lesion has been recorded while marked and moderate improvement reported in(%30),(%40)of actinic lesions respectively and only (%30) of actinic

lesions showed slight improvement .In contrast ,in Group B %30 H2O2, out of twenty actinic patches %60 of them showed clinically clearance and slight improvement was recorded in %20 of lesions, there were statistically significant differences between two groups ; p-value=0.000).

Table (4) : The association between in (H2O2 20% & H2O2 30%) and Response / No. patches

Response / No. patches	Group A (H2O2) 20%		Group B (H2O2) 30%		Total		Significant Test
	Fr.	%	Fr.	%	Fr.	%	
Clinically Cleared	0	0.0	12	60.0	12	30.0	$\chi^2 = 20.8$ P=0.000
Marked improvement	6	30.0	4	20.0	10	25.0	
Moderate improvement	8	40.0	0	0.0	8	20.0	
Slight improvement	6	30.0	4	20.0	10	25.0	
Total	20	100.0	20	100.0	40	100.0	



Figure(1): the association between in (H 2O2 20% and H 2O2 30%)and response/No. Patches

Table (5) compares the response of therapy in between both groups in relation to grades of actinic, as it is clear from the table 60% of actinic lesions in group B (%30) H2O2 clinically cleared which were (grade I and grade II) actinic while marked improvement were recorded in %20 of lesions which were all grade II actinic only %20 of lesions showed slight improvement which were grade III actinic. In comparison to group A (%20) H2O2 no clinically cleared actinic

lesion reported while marked improvement were recorded in %30 of lesions which were all grade I actinic, (%40) of lesions showed moderate improvement which were (grade I & II) and slight improvement were observed in %30 of lesions which were (grade II & III). Statistically there were significant differences (or association) between (I, II and III) grades in response of (H2O2 20%: p-value=0.002), H2O2 30% (p value=0.000) and in general (p-value=0.0000).

Table (5): The Association between response of (H2O2 20% & H2O2 30%) and grade

Response / No. patches		Grade						Total		Significant Test
		I		I		I				
		Fr.	%	Fr.	%	Fr.	%	Fr.	%	
A (H2O2) 20%	Clinically Cleared	0	0.0	0	0.0	0	0.0	0	0.0	$\chi^2 = 17.25$ P=0.002
	Marked improvement	6	75.0	0	0.0	0	0.0	6	30.0	
	Moderate improvement	2	25.0	6	60.0	0	0.0	8	40.0	
	Slight improvement	0	0.0	4	40.0	2	100.0	6	30.0	
Total		8	100.0	10	100.0	2	100.0	20	100.0	
B (H2O2)	Clinically Cleared	6	100.0	6	60.0	0	0.0	12	60.0	$\chi^2 = 24.001$ P=0.000
	Marked	0	0.0	4	40.0	0	0.0	4	20.0	

30%	improvement									
	Moderate improvement	0	0.0	0	0.0	0	0.0	0	0.0	
	Slight improvement	0	0.0	0	0.0	4	100.0	4	20.0	
Total		6	100.0	10	100.0	4	100.0	20	100.0	
General	Cleared	6	42.9	6	30.0	0	0.0	12	30.0	$\chi^2 = 25.686$ P=0.000
	Marked improvement	6	42.9	4	20.0	0	0.0	10	25.0	
	Moderate improvement	2	14.2	6	30.0	0	0.0	8	20.0	
	Slight improvement	0	0.0	4	20.0	6	100.0	10	25.0	
Total		14	100.0	20	100.0	6	100.0	40	100.0	

Table (6) indicates the association between (H2O2 20% & H2O2 30%) and side effect of patients. Majority of patients (85%) has recorded burning sensation, irritation and

transient erythema, while no scarring, pigmentation, atrophy has been recorded.

Table (6). The association between (H2O2 20% & H2O2 30%) and side effect of patients

Side effect of patients		Group A (H2O2) 20%		Group B (H2O2) 30%		Total		p value
		Fr.	%	Fr.	%	Fr.	%	
Buring	No	1	10	2	20	3	15	0.392 P=0.531
	Yes	9	90	8	80	17	85	
Erythema	No	2	20	0	0.0	2	10	2.222 P=0.136
	Yes	8	80	10	100	18	90	
Irritation	No	4	40	0	0.0	4	20	5.00 P=0.025
	Yes	6	60	10	100	16	80	
Atrophy	No	10	100	10	100	20	100	No difference
	Yes	0	0.0	0	0.0	0	0.0	
Scarring	No	10	100	10	100	20	100	No difference
	Yes	0	0.0	0	0.0	0	0.0	
Pigmentation	No	10	100	10	100	20	100	No difference
	Yes	0	0.0	0	0.0	0	0.0	
Total		10	100	10	100	20	100	



Group A %20 H2O2



Group B %30 H2O2

Discussion:

Actinic keratoses (AK) are common precancerous cutaneous lesions caused by chronic ultraviolet exposure that appear on sun-exposed areas, most notably the face and head. It is now evident that AK lesions can evolve into SCC at any time.^{13,14} so closely monitor and manage every lesion, as supported by many authors. The efficacy of 20% and 30% H₂O₂ in the treatment of actinic keratosis was evaluated and compared in this study. Regarding the demographics of patients, twenty cases were

enrolled in this study, with their ages ranging from 45 to 70 years with mean age 65.6 ± 9.4 years which means the actinic keratosis rate is higher in older people. This finding is consistent with the findings of by Li, who described an increased risk of actinic keratosis with age.¹⁶ Most of the participants in the study (55%) were male, and the results are in line with a study done by Yaldiz, who found that actinic keratosis prevalence is higher in males in comparison to females.¹⁷ Nine out of twenty (45%) patients were outdoor workers (farmers, taxi

drivers), which explains its relationship to sun exposure. This finding is consistent with a study conducted in 2019 by Grandahl K, which found: "Outdoor work is associated with an increase in the occurrence of facial wrinkles and actinic keratosis from solar radiation."¹⁸The majority of cases (45% and 30%, respectively) had skin phototypes II and III, which is similar to a study published by Acar.¹⁹Both groups, including all forty lesions in the study, showed reductions in both hyperkeratosis and the size of the clinically observed lesions; in fact, we have no cases without any response. In regards to comparison between two groups, Group B (%30 H₂O₂) shows that out of twenty actinic lesions, 60% of them reported total clinical clearance. Meanwhile, no clinically totally cleared lesion had been recorded in group A (%20 H₂O₂). In addition, a slight improvement in response was recorded in 30% of actinic lesions in Group A compared to 20% in Group B. There was a statistically significant difference in response between the two groups (p-value =0.000). These findings are in line with a publication by Sadeghinia A²⁰, who compared the efficacy of %35 H₂O₂ with cryotherapy in AK, which showed that both groups had marked improvement in their lesions with no significant difference between the two groups. Although the exact mechanism by which hydrogen peroxide appears to treat AK has not been fully understood, it is possible that the oxidant effects of H₂O₂ via reactive radicals damage the skin and disrupt the epidermis. Notably, normal skin is unaffected by the effects of H₂O₂, whereas altered cells are more vulnerable.¹⁵

Furthermore, in a case series study, 33% hydrogen peroxide used as a neoadjuvant treatment in the surgical excision of non-melanoma skin cancers (NMSC) revealed that hydrogen peroxide significantly reduced the size of all the lesions included in this study. Particularly, lesions' length and width

were each reduced by a mean of 50% and 48%, respectively.²¹If we compare our results with other treatments of AK, in a prospective study of the use of cryosurgery for the treatment of actinic keratoses, the overall individual complete response rate was 67.2%.²²Another commonly used topical treatment for actinic keratosis is 5-FU cream. Although topical 5-FU treatment has been shown to have cure rate more than 90% in patients who use and tolerate full courses of therapy²³, side effects like irritation, inflammation, erythema, erosions, and ulceration may lead patients to stop therapy early, which lowers cure rates²⁴. An average AK lesion response rate of 87.8%±2.2% and an average complete patient response rate of 62.5%±12.0% were found in a meta-analysis of seven studies using topical 5-FU, all of which lasted 2-4 weeks.²⁵Imiquimod cream is also frequently applied topical treatment of actinic keratosis, 25 patients with 5–20 distinct actinic keratoses were treated three times a week for four weeks, then had four weeks off as part of Salasche et al.'s open-label trial with imiquimod 5% cream. 82% of lesions, including subclinical lesions that were discovered by imiquimod treatment, completely cleared.²⁶Despite, there are number of studies demonstrate efficacy of hydrogen peroxide in treatment of warts, molluscum, Neoadjuvant treatment in the surgical excision of nonmelanoma skin cancers²¹ but, up to our best knowledge only one study done on efficacy of hydrogen peroxide in actinic keratosis²⁰, no further studies available. Regarding the response rates based on the various grades of actinic keratosis, the study's result was that the patient subgroup that would most benefit from treatment was those who had thin actinic keratosis grades I or II, Also finding showed that in both groups slight improvement response was more recorded in grade III actinic lesions, and statically was



significant difference in response according to grades between two groups (p-value=0.000) which may be explained by thick impacted and distorted keratinocytes that do not allow easy distribution and penetration inside all layers. This result is similar to a study published by Neittaanmäki-Perttu N on photodynamic therapy in actinic keratosis, which showed grades I and II actinic lesions had a significantly greater response compared to thicker grades.²⁷ Both patient groups tolerated treatment well, with only minor transient discomfort, redness, and burning sensations and no unsightly pigmentation or scarring reported. This finding is similar to other studies which were done on application of Hydrogen peroxide in different conditions.^{20, 21} The safety profile of hydrogen peroxide has been confirmed in previous investigations as well.¹¹ Overall, our preliminary studies show hydrogen peroxide is a noninvasive, safe, effective topical treatment for actinic keratosis and its efficacy and rate of clearance increased if higher concentration of H₂O₂ %30 used compared to %20 H₂O₂. Therefore, it could be used as an alternative to current destructive or ablative modalities such as cryotherapy, which can cause scarring and pigmentation in addition to causing pain. Furthermore, studies with larger population sample are required in evaluation of its efficacy.

Conclusion:

In this comparative clinical trial, we found that both concentrations of hydrogen peroxide (%20 & %30) was safe and effective treatment of actinic keratosis but, the results and clearance rate were better with higher concentration Hydrogen peroxide.

Conflict of interest

There were no conflicts of interest.

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