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Comparing efficacy and safety of potassium hydroxide 5% solution with 5-fluorouracil cream in patients with actinic keratoses: a randomized controlled trial

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Title: Comparing efficacy and safety of potassium hydroxide 5% solution with 5-fluorouracil cream in patients with actinic keratoses: a randomized controlled trial.

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Abstract

Background: Actinic keratosis (AK) is a pre-cancerous skin lesion, associated with development of squamous cell carcinoma. Current treatment options are limited

Objectives: To compare the efficacy and safety of topical 5-fluorouracil cream (5-FU) and potassium hydroxide 5% (KOH) in the treatment of AK.

Methods: Eighteen patients with AK applied KOH solution or 5-FU on each side of their scalp/face, randomly. The efficacy and safety of these treatments were compared.

Results: Thirteen (118 lesions) and ten (83 lesions) patients were successfully followed for one and three months, respectively. After one month, KOH showed a better clinical response (81% vs. 58%; P-value=0.007) and dermoscopic response (KOH, 65% vs. 5-FU, 46%; P-value=0.04); while no differences were noted after three months (clinical response, 83% vs.70%, P-value=0.1; dermoscopic response, 76% vs. 59%, P-value=0.1). No significant differences in the recurrence rate of the lesion between the two groups were noted at the end of the third month (P-value=0.5). Regarding the safety of the treatments, the risk of developing erythema, scaling, sand swelling was higher in 5-FU group (P-value<0.0001, for all), while more patients in KOH group had erosion and ulcer (P-value<0.001 for both). KOH was up to 96% less expensive than 5-FU.

Limitations: Low number of patients and short-term follow-up limited the analysis.

Conclusion: KOH solution offers a faster and less expensive resolution of AK lesions than does 5-FU.

Ethics approval number: IR.TUMS.TIPS.REC.1397.010 (the Pharmaceutical Sciences Research Institute of Tehran University of Medical Sciences' ethics committee)

Clinical Trial Code (IRCT.ir): IRCT20180909040978N1

Introduction

Major treatments for actinic keratosis (AK) include two types: destructive modalities such as curettage, and cryotherapy; and non-destructive agents including topical creams such as 5-fluorouracil cream 5% (5-FU) (1-5). Destructive modalities can be associated with different adverse effects such as dyspigmentation, bulla formation, infection, and scarring (6-11). 5-FU is approved by the U.S. Food and Drug Administration (FDA) for the treatment of AK (12, 13). However, 5-FU is associated with erythema, crust formation, and bleeding; its effectiveness decreasing in the long run (14, 15). Potassium hydroxide (KOH) is a keratolytic agent that is used in the treatment of skin lesions such as warts, molluscum contagiosum, and plantar callus (16-19). KOH is an effective, safe, and inexpensive drug that can easily dissolve keratin and penetrate skin due to its alkaline nature (20).

Considering the limited available therapeutic options for treating AKs, further practical, economical, and reliable therapeutic options requiring fewer skills are needed to open some avenues into better management of AK patients. In this randomized controlled trial (RCT), we aimed to evaluate the efficacy and safety of KOH 5% solution in AK patients, comparing the results with 5-FU.

2. Materials and Methods

2.1 *Study population*

Patients at least 18 years of age, who were newly diagnosed cases with a minimum of two AK on each side of the scalp and/or face were identified from the dermatology clinics of Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran. Patients with a history of allergy to 5-FU or KOH were excluded. Diagnosis of AK was based on clinical examination, by two dermatologists, and pathological evaluation in suspicious cases. Patients were asked to sign a consent before recruitment. This study was performed according to the Helsinki declaration and is approved by the Pharmaceutical Sciences Research Institute of Tehran

University of Medical Sciences' ethics committee (**IR.TUMS.TIPS.REC.1397.010**). The trial is also registered in the Iranian Clinical Trial Registry (**IRCT20180909040978N1**).

2.2. Study design and treatments

From November 2018 to December 2018, patients who met the inclusion criteria were assigned to be treated with KOH 5% solution or 5-FU (Efudix, Meda Pharmaceuticals Ltd) by block randomization. KOH 5% in water was prepared by Razi Hospital's laboratory of compounding drugs. Patients were trained to apply KOH solution for one side of their scalp or face and 5-FU cream for the other side. They were told to apply the medications once a night for four weeks. At baseline, demographic information, patients' characteristics, and skin color (using the Fitzpatrick scale) were documented. Additionally, skin photodamage was recorded in four categories: 1 (very severe), 2 (severe), 3 (moderate), and 4 (mild).
In the case of 5-FU, patients were asked to use it on clean skin and avoid washing the area for at least 12 hours after application. For the KOH group, patients were trained to completely cover normal skin with a thick layer of Zinc Oxide ointment to prevent its exposure to normal skin and to apply KOH with a cotton-tipped applicator precisely on the lesion (Figure 1). Daily KOH application was continued until erosion formation. In the case of ulcer formation, the treatment was stopped for a few days, and the patients were recommended to apply Zinc Oxide ointment on the affected area and to resume the treatment after the complete resolution of the ulcer. Patients were provided a treatment manual and a telephone number available 24/7 for any questions.

2.3. Treatment assessment

Patients were asked to return at 2, 4, 8, and 12 weeks for follow-up. Photography with a camera and dermoscopic images with FotoFinder Medicam 1000 (FotoFinder Systems GmbH, Bad Birnbach, Germany) from lesions were taken for each patient at baseline, at the

end of the first and the third months. Two dermatologists, blinded regarding the treatment sides, evaluated the outcomes based on clinical examination and dermoscopic images. Clinical response was defined as lesion resolution, characterized by the complete disappearance of skin roughness through palpation of the location of lesions by dermatologists.

Patients were also monitored for dermoscopic changes of lesions, including yellow scale, white scale, pseudo-network pattern, pigmented dots, and linear-wavy vessels during and after treatments. Dermoscopic response for each lesion was defined as the resolution of all dermoscopic features. Short-term side effects of 5-FU or KOH 5% were monitored until the end of the third month. Adverse effects were rated by evaluators using a visual analog scale graded from 0 to 10.

2.4. Sample size

The sample size was calculated utilizing G-power software based on the McNemar test. Considering 95% confidence (0.05 error probability), with a power of 80%, an effect size of 2, and the proportion of discordant pairs equal to 0.6, a total of 120 lesions were considered.

2.5. Statistical analysis

Mean and standard deviation (SD) were reported for quantitative variables and frequency for qualitative variables. Chi-square and McNemar tests were used to analyze data. Statistical calculations were performed using SPSS, version 24 (IBM Corp. (2016). IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp; Released 2016)), and R software using nlme package (30).

3. Results

3.1. *Patients' characteristics*

Out of 18 eligible patients (with 148 lesions), 13 patients (with 118 lesions) completed the treatment procedures and were followed until the end of the first month, but 3 (with 35 lesions) did not return for the third month's follow-up (Figure 2).

All included patients were men, with an average age of 75±7.1 years (range 57-84) and mean of lesions 8.2±3.1 (range 4 to 15) lesions on each side. At the end of the first month, out of 118 total lesions, 110 (93%), five (4.2%), and three (2.5%) were located on the scalp, temporal regions of the face, and nose, respectively. Sixty-eight lesions (58%) were treated by KOH solution and 50 (42%) with 5-FU cream. However, at the end of the third month, out of 83 lesions, 46 (55%) were treated by KOH solution and 37 (45%) with 5-FU cream (Table 1).

3.2. Efficacy

At the end of the first month, 55 out of 68 lesions (81%) treated with KOH, and 29 out of 50 (58%) treated with 5-FU completely resolved (P-value=0.007, Odds ratio: 3.1). Complete dermoscopic response occurred in 44 (64.7%) and 23 (46%) of the lesions in KOH and 5-FU arms, respectively (P-value= 0.04, Odds ratio: 2.2). At the end of the third month, clinical responses were observed in 38 out of 46 lesions (83%) and 26 out of 37 (70.%) in KOH and 5-FU, respectively (P-value=0.2). In addition, dermoscopic response was recorded in 35 (76%) of lesions in KOH and 22 (59%) in 5-FU arms (P-value=0.1, Figure 3,4, Table 2). Meanwhile, the clinical and dermoscopic response rates were found to be correlated in both the first and the third months by 73.7% and 84.3%, respectively (first month: P-value<0.001, kappa=0.4, moderate; third month: P-value<0.001, kappa=0.6, substantial).

Out of 118 lesions, 83 had been visited in both the first and the third months. At the end of the first month, the number of AK lesions was reduced by 80% (37 from 46) and 65% (24 from 37) (P-value=0.1, Figures 3 and 4). However, 8.0% (3 from 37) in the KOH group and 4% (1 from 24) of the resolved lesions in 5-FU sides had recurrence during the third month (P-value=0.5, Table 3). Of unresolved lesions during the first month in KOH and 5-FU treated lesions, 44% (4 from 9) and 23% (3 from 13) healed in the third month (P-value=0.4). However, 11% (5 out of 46) and 27% (10 out of 37) of total lesions did not respond at the end of the first and the third months (P-value=0.06, Table 3).

Dermoscopic of yellow scale (P-value <0.0001), white scale (P-value <0.0001), and pseudo-network pattern (P-value <0.0001) improved in both groups, but no significant differences were observed for these features between the two treatments at the end of the first month (P-value=0.6, P-value=0.3, and P-value=0.2, respectively). Neither treatment reduced pigmented dots (KOH, P-value: 0.02; 5-FU, P-value=1) or linear-wavy vessels (KOH, P-value: 1; 5-FU, P-value= 0.6); there was no significant differences between the two groups for these two features (P-value=0.5 for KOH; P-value=0.3 for 5-FU).

Although, the dermoscopic outcome at the end of the third month, for each of yellow scale, white scale, and pseudo-network pattern dermoscopic features improved in both groups (P-value <0.0001 for all), no differences were noted between treatments (P-value=0.9, P-value=0.3, and P-value=0.8, respectively). Additionally, dermoscopic features of pigmented dots and linear-wavy vessels did not change after the three-month treatment (KOH, P-value: 0.2; 5-FU, P-value=0.6; KOH, P-value: 0.2; 5-FU, P-value=0.6, respectively) nor between the two groups (P-value=0.5, P-value=0.8, respectively) at the end of the third month (Table 4).

At the end of the first and the third months, neither clinical response nor dermoscopic response rates were associated with radiotherapy, sun exposure, or Fitzpatrick skin type in any of the treatment groups.

3.3. Safety profile

The chance of developing erythema in the 5-FU group was 24 (48%) which was higher than KOH group [13 (19%)] (95%CI:1.7-8.9; P-value<0.0001). Scaling and swelling were found in 29 (58%) and 10 (20%) of patients treated with 5-FU which was also statistically higher compared to patients treated with KOH [4 (5.9%) and 0 (0%), respectively],(95% CI: 6.7-70.2 and 2-616.2; P-value<0.0001 for both). More patients treated with KOH had erosion (21, 30.9%) and ulceration (67, 98.5%) than with 5-FU (4, 8% and 4, 8%, respectively, 95% CI: 1.6-16.1 and 83.4-7092.2, respectively and P-value<0.0001 for both). However, there was no relationship between the incidence of adverse effects and the type of treatment for developing crust (P-value=0.5). Tables 5 and 6 summarize the prevalence and severity of the side effects of the treatment based on VAS.

4. Discussion

In this randomized controlled trial, both clinical and dermoscopic responses of AK improved more with KOH solution compared to 5-FU at the end of the first month, although we did not find any differences at the end of the third month. Clinical examination showed a higher response rate than dermoscopic evaluation in both groups. However, the clinical and dermoscopic response rates were correlated in both the first and the third months.

We did not find any difference between the two therapeutic methods in the improvement of dermoscopic features. However, yellow scale, white scale, and pseudo-network pattern, but not pigmented dots and linear-wavy vessels improved in both groups at the end of the first and the third months. Pigmented dots and vascular features are related to structures located in the superficial and deep dermis. The effects of the topical treatments may not penetrate deep enough to resolve these features. Furthermore, comparing results at the end of the first and

the third months, none of the improved dermoscopic features relapsed and the therapeutic effects of both treatments continued.

Evaluation of drug-related side effects revealed no difference in crust formation between the two groups. However, 5-FU had higher rates of erythema, scaling, and swelling. In contrast, erosion and ulcer formation was more common with KOH treatment. The therapeutic effects of KOH are through tissue destruction; erosion and ulceration are a part of its therapeutic mechanism.

According to S3 guidelines for the treatment of AK, two main strategies are recommended in the management of AK patients; 1) lesion-directed treatments, which are recommended to be used for not more than 5 lesions (single AK lesions); 2) field-directed treatments, which are used for more than 5 lesions (multiple AK lesions) (12). In the view of the direct and destructive function of KOH, it cannot be recommended for the latter approach. On the other hand, 5-FU is a field-directed strategy and is highly recommended to be used in cases with multiple AK on photodamaged skin. Although KOH cannot be recommended for multiple AK lesions, it seems a potential treatment in single AK lesions. Given cost-effectiveness, KOH solution is relatively cheaper than 5-FU cream, in addition to its more convenient access.

There are some limitations in our study. First, a relatively low number of included patients may have affected the results of the study. Second, we did not use the Actinic Keratosis Area and Severity Index (AKASI), which has been introduced recently to evaluate AK severity (21). Also, short follow-up time, lack of female patients, loss to follow up, and patients' old age (which could have affected the proper application of the treatment) were other limitations of the present study.

In conclusion, the efficacy of KOH 5% solution in AK lesions was not significantly different from that of 5-FU. However, KOH provided higher clinical and dermoscopic response rates

after one month and provides an effective, safe, and inexpensive modality for the treatment of single AK lesions.

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Table 1. Characteristics of included patients with actinic keratosis.

		Included patients
Gender (n)	Male	13 (118 lesions)
	Female	0
mean age ± SD; range (years)		74.93± 7.1; 57-84
Number of lesions per patient		8.22 ± 3.1 (range 4 to 15)
Fitzpatrick skin types (n; %)	III	23(19.5)
	IV	95(80.5)
Locations (n; %)	Nose	3 (2.6)
	temporal regions of the face	5 (4.2)
	Scalp	110 (93.2)
Past Medical History (n; %)	other skin diseases	1 (7.7)
	Non-Melanoma Skin Cancer	5 (38.5)
Radiotherapy history (patients, lesion; %)		6, 56 (47.5)
Sun exposure grade* (patients, lesion; %)	I	6, 57 (48.3)
	II	1, 8 (6.8)
	III	3, 29 (24.6)
	IV	3, 24 (20.3)

* Four categories: 1 (very severe), 2 (severe), 3 (moderate), and 4 (mild).

Table 2**.** The percentage of changes in clinical response, during the time, for the two treatment groups.

	Treatment	After 1 Month	After 3 Months
Clinical Response	KOH5% Solution	80.8%	82.6%
	5-Fluorouracil Cream	58%	70.3%
P-value		0.007	0.184
Dermoscopic response	KOH5% Solution	64.7%	76.08%
	5-Fluorouracil Cream	46%	59.45%
P-value		0.043	0.153

Table 3. The trend of treatment response in patients during a three-month follow-up. Group A refers to those whom theirs lesions resolved after the end of the first month but experienced recurrence after a third-month evaluation. Group B refers to patients who did not respond after the first month, while responded at the end of the third month. Group C shows patients who responded neither after the first nor the third months.

	A	B	C
KOH	8.02% (3 from 37)	44.43% (4 from 9)	10.87% (5 out of 46)
5-FU	4.17% (1 from 24)	23.08% (3 from 13)	27.03% (10 out of 37)
P-value	0.544	0.376	0.057

Table 4. The Percentage of Changes in Dermoscopic Features, During the Time, for the Two Treatment Groups. *Abbreviations*: KOH 5%, Potassium hydroxide; 5-FU, 5-fluorouracil cream 5%.

Dermoscopic Feature	Treatment	Before Treatment (118)	After 1 Month	P-value	Before treatment (83)[$]	After 3 Months	P-value
Yellow Scale[*]	KOH 5%	58%	19%	Value 0.256	60.9%	17.4%	0.887
	5-FU	64%	28%		62.2%	16.2%	
White Scale[*]	KOH 5%	43.7%	9.9%	0.137	47.8	6.5%	0.283
	5-FU	53.8%	19.2%		59.5	13%	
Pseudo-Network Pattern[*]	KOH 5%	47.1%	7.4%	0.238	47.8	6.5%	0.832
	5-FU	48%	14%		48.6	5.4%	
Pigmented Dots[#]	KOH 5%	23.5%	10.3%	0.538	13	4.3%	0.474
	5-FU	12%	14%		2.7	8.1%	
Linear-Wavy Vessels[#]	KOH 5%	8.8%	7.4%	0.773	13	6.5%	0.781
	5-FU	10%	6%		13.5	8.1%	

* These dermoscopic features had been improved significantly after the first and third months (P-value < 0.0001).

These dermoscopic features were not significantly different after the first and third months (P-value > 0.05).

$ Due to the loss of follow-up in three patients, the total number of patients at baseline for analysis regarding the end of the third month became ten patients (83 lesions).

Table 5. Comparison of the safety profiles of KOH 5% and 5-Fluorouracil cream groups during the study.

	KOH 5% group (n=68) N (%)	5-Fluorouracil cream group (n=50) N(%)	Total (n=118) N(%)	P-value
Erythema	13 (19.1)	24 (48)	37(31.4)	<0.0001
Crust	16 (23.5)	9 (18)	25(21.2)	0.556
Scaling	4 (5.9)	29 (58)	33(28)	<0.0001
Swelling	0	10 (20)	10(8.5)	<0.0001
Erosion	21 (30.9)	4 (8)	25(21.2)	0.001
Ulcer	67 (98.5)	4 (8)	71(60.2)	<0.0001

Table 6. The severity of the safety profiles of KOH 5% and 5-Fluorouracil cream groups during the study.*

	KOH 5% group	5-Fluorouracil cream group (mean ± SD)	P-value
	(mean ± SD)		
Erythema	2.21 ± 1.25	2.43 ± 1.55	0.385
Crust	1.64 ± 1.08	2.50 ± 1.56	0.061
Scaling	0.43 ± 0.65	1.64 ± 1.00	**0.001**
Erosion	4.14 ± 1.83	3.29 ± 1.81	0.089
Ulcer	2.00 ± 1.11	0.14 ± 0.54	**<0.0001**
Burning	2.71 ± 1.63	2.14 ± 1.41	0.088
Pruritus	0.14 ± 0.36	0.93 ± 1.07	**0.015**

*The severity of reactions has been calculated based on the Visual Analogue Scale (VAS) ranging from 0 to 10.

Figure legend

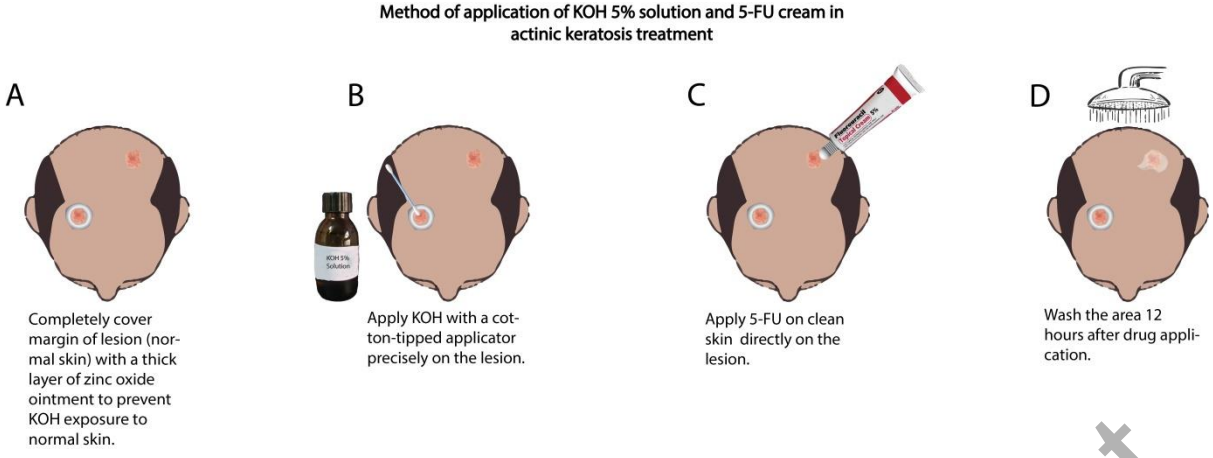

Figure 1. The application method of KOH 5% solution and 5-FU cream.

Patients were asked to 5-FU use it on clean skin and avoid washing the area for at least 12 hours after application. For the KOH group, patients were trained to completely cover normal skin with a thick layer of Zinc Oxide ointment to prevent its exposure to normal skin and to apply KOH with a cotton-tipped applicator precisely on the lesion

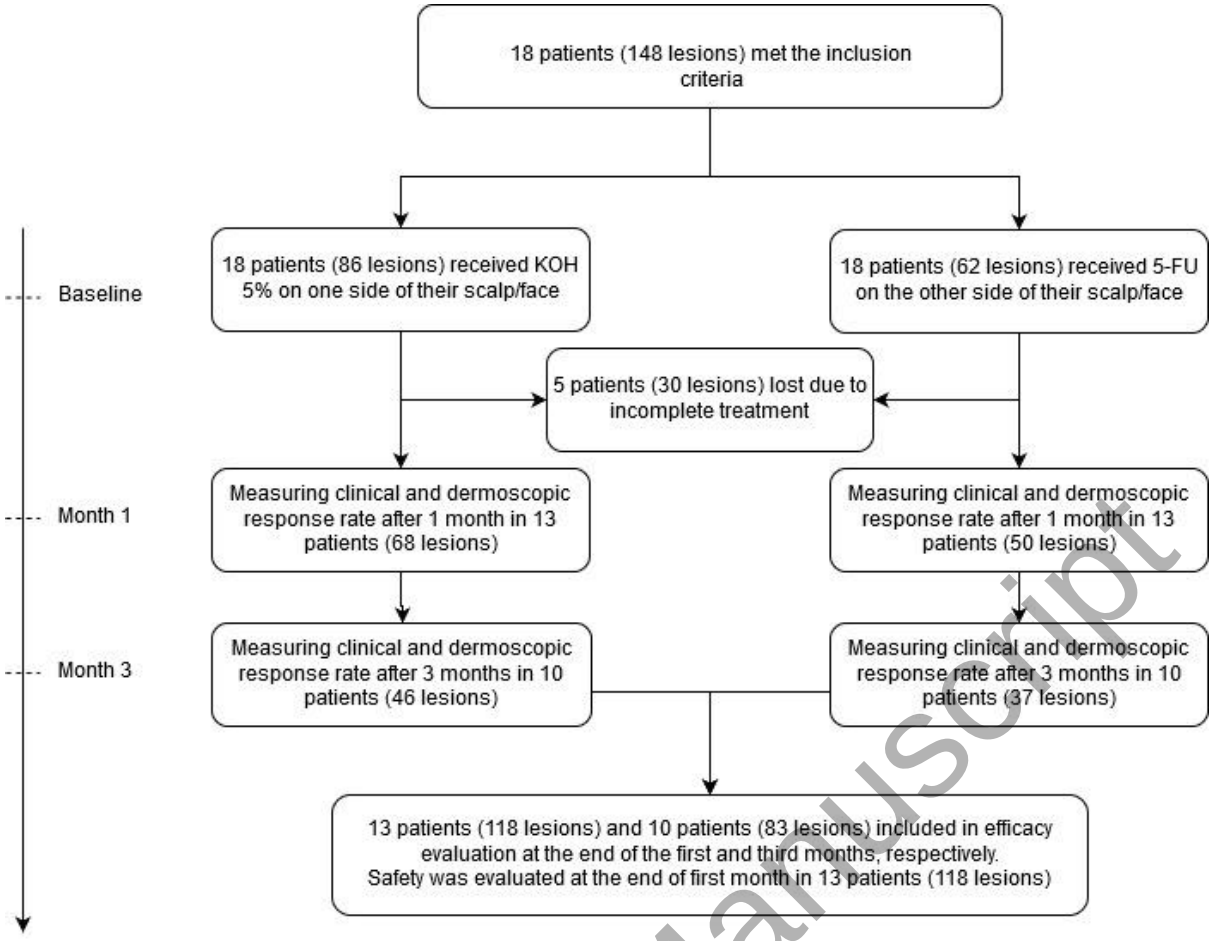

Figure 2. Randomization and Follow-up among the Patients in the Trial.

Eighteen patients (with 148 lesions) were recruited at the beginning, 5 patients (30 lesions) lost to follow-up, while 13 patients and 10 completed the treatment procedures and were followed until the end of the first and the third months.

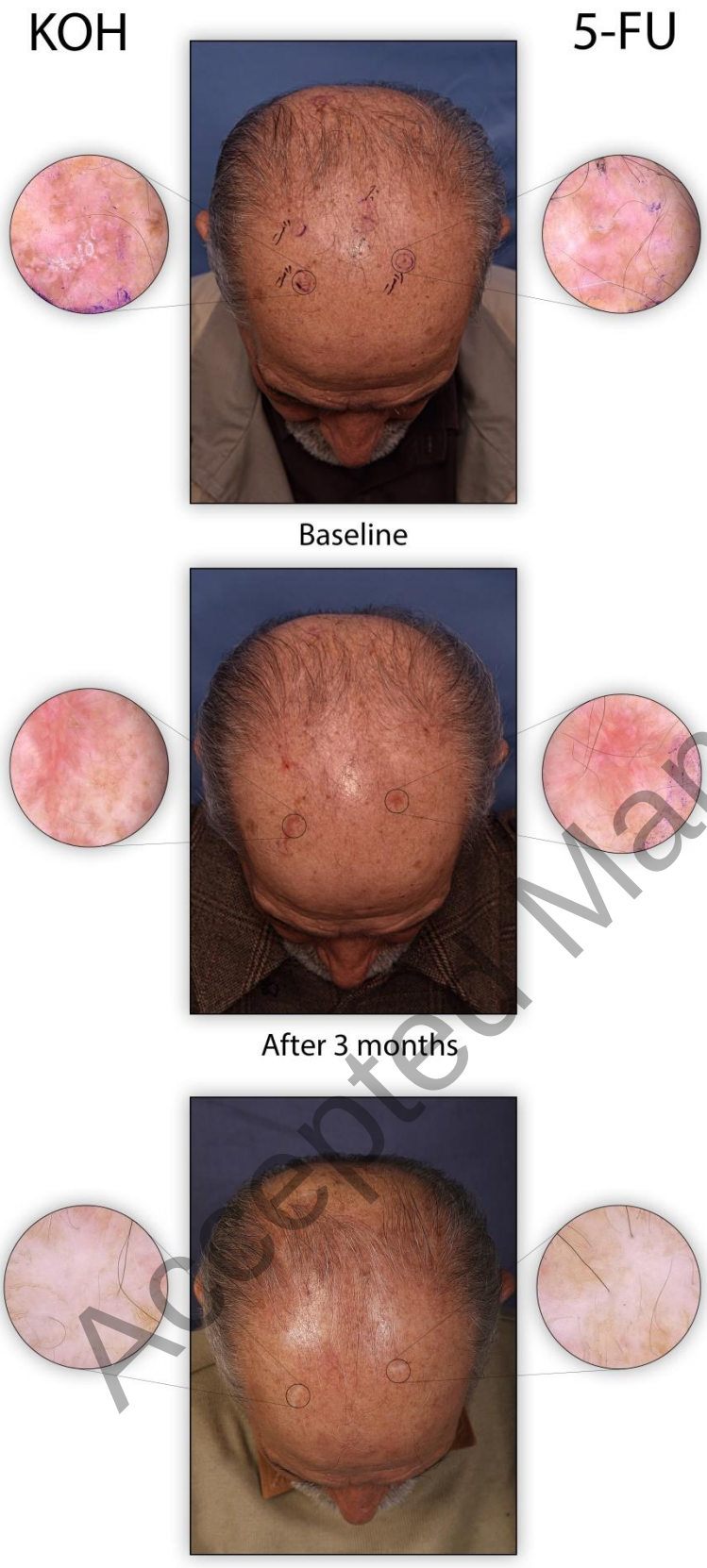

Figure 3. “A 69-year-old man with multiple actinic keratoses was treated with KOH 5% and 5-FU 5%.

As seen in dermoscopic images at baseline, yellow follicular scale, white scale, and pseudo-network pattern are seen in the KOH-treated lesion and follicular yellow and white scale in the 5-FU-treated lesion. In the dermoscopic images three months after the treatment, a noticeable improvement is seen in yellow and white scales in both images, while linear-wavy vessels did not change and became more prominent. No remnant of the previous lesions was seen after one year.”

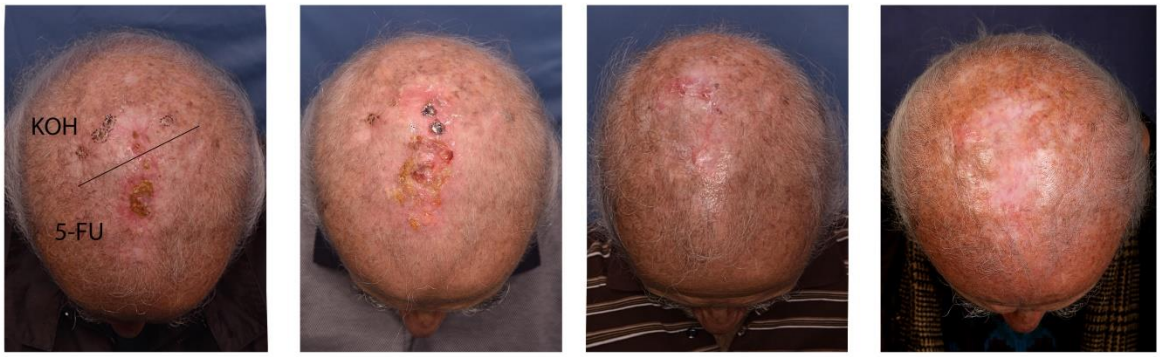

Figure 4. “A 71-year-old man with multiple actinic keratoses treated with KOH 5% (above the line) and 5-FU 5% (below the line).”

At the end of the first month, erosions and ulcers are evident in the KOH part and a diffused erythema and crust formation are seen in the 5-FU part. The kin adverse effects and actinic keratoses are improved at the end of the third month and there is no evidence of disease recurrence at the end of the first year in both parts of the treatment.