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Chemical Peels as Field Therapy for Actinic Keratoses: A Systematic Review

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BACKGROUND Actinic keratoses (AKs) are a common premalignant cutaneous neoplasm and can progress to squamous cell carcinoma. A variety of treatment options are available for field therapy of diffuse AKs.

OBJECTIVE This review systematically analyzes the use of chemical peels for treatment of AKs.

MATERIALS AND METHODS A systematic review of PubMed was performed searching from 1946 to March 2020 to identify the literature on chemical peels for AKs.

RESULTS Of the 151 articles identified, 5 met inclusion criteria for review. Four of the reviewed articles demonstrated the efficacy of chemical peels in reducing AK count and minimal adverse effects. In some studies, chemical peels exhibited potential to prevent additional AK formation and development of keratinocyte carcinomas.

CONCLUSION Chemical peels are an efficacious and affordable treatment option for field treatment of AKs. With improved patient tolerance and adherence, chemical peels are an attractive option for field therapy of AKs for both dermatologists and patients.

Actinic keratoses (AKs) are premalignant cutaneous lesions, typically presenting on sun-exposed sites such as the face, scalp, and extremities.[1] They are characterized histologically by dysplastic keratinocytes, with potential progression to squamous cell carcinoma (SCC), and thus, early detection and treatment are paramount.[2,3] A 2012 Cochrane Review concluded the most effective, evidence-based treatments for AKs include cryotherapy, diclofenac, 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, laser resurfacing, trichloroacetic acid chemical peel, aminolevulinic acid photodynamic therapy (ALA-PDT), and methyl aminolevulinate PDT.[4]

The choice of field therapy for diffuse AK depends on a variety of factors, including patient compliance, cost, tolerance for clinical recovery or "downtime," and efficacy. Although most dermatologists agree on the importance of field treatment, cryotherapy still remains the standard of care for treatment of AKs. In a survey of over 400 physicians in 8 countries, 90% of physicians prescribe the treatment requiring the shortest duration of application and the highest rate of patient compliance.[5] Therefore, an in-office, single visit procedure may be preferred by patients and physicians alike when compared with a prolonged topical therapy.

Chemical peels are indicated in the management of extensive, confluent AKs with the goal of replacing atypical keratinocytes with the normal epidermis and decreasing the rate of AK recurrence over large surface areas efficiently.[6,7] Chemical peels offer a one-time treatment for patients which circumvents the issue of patient compliance, required by topical therapies. Patients report preference for the tolerability of treatment with chemical peels and the shorter downtime compared with other field treatments.[8] This article systematically evaluates the literature on the safety and efficacy of chemical peels for treatment of diffuse AKs.

Methods

The National Library of Medicine's PubMed database was queried to identify studies on chemicals peels for treatment of AKs using the search terms "chemical peel," "chemexfoliation," "chemabrasion," "actinic keratosis," "actinic damage," "keratinocyte carcinoma," "squamous cell carcinoma," and "basal cell carcinoma." All randomized and nonrandomized trials, cohort studies, case reports, and case series in English language were included with a publication date range from 1946 to March 18, 2020. Inclusion criteria also required studies to report pre-treatment and post-treatment AK counts. References from the retrieved articles were also reviewed for inclusion.

Articles were considered for inclusion based on the title and abstract.

Results

A total of 151 articles were retrieved, of which 146 were excluded. Five articles were identified for further review. Of

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the 5 articles, one article investigated the use of glycolic acid peels,[9] 2 articles studied combination Jessner's and 35% trichloroacetic acid (TCA) peels,[10,11] and 2 articles studied TCA peels (Table 1).[12]

Study Design

Glycolic Acid Peels

The efficacy of glycolic acid peels for the treatment of AKs was studied in a split-face study with 18 patients.[9] Glycolic acid was applied on the skin for 2 minutes and neutralized with water for 2 minutes. A thin layer of 5-FU solution was then applied to one side of the face. This regimen was performed weekly for 8 treatments.

Jessner's and 35% Trichloroacetic Acid Peels

Lawrence and colleagues[10] compared the efficacy of Jessner's and 35% TCA peel compared with 5-FU twice daily for 3 weeks in a split-face study. The combination peel was applied until a faint frost was attained. These patients were followed for one year and re-evaluated again at 32 months, which was published in a subsequent study.[10,11]

Trichloroacetic Acid Peels

Two studies investigated the efficacy of TCA peels compared with other field treatments.[8,12] In the study by Hantash and colleagues, 27 patients were randomized to 1 of 3 treatment arms: carbon dioxide laser resurfacing, 30% TCA peel, or 5-FU twice daily application for 3 weeks. Patients who received carbon dioxide laser received 2 passes, the first pass at 6 W and second pass at 5 W. For the chemical peel arm, 30% TCA was applied until a Level 2 frost was noted. AK count was performed 3 months after treatment, and patients were followed for up to 5 years to measure the incidence of new KCs.

Thirty-five percent TCA was also compared with ALA-PDT in 28 patients.[12] Thirty-five percent TCA was applied until a level 1 frost was achieved. 20% ALA was applied

TABLE 1. Studies Included in Systematic Review of Chemical Peels for Treatment of Actinic Keratosis

Author	Year	Study Type	Chemical Peel	Intervention	Application	Mean Reduction ±SD	Follow-Up Period
Marrero et al.[9] N = 18	1998	Prospective, split-face	70% glycolic acid + 5-FU	Glycolic acid peel alone weekly × 8 treatments	2-minute contact until neutralization	19.7%*	6 mo
				Glycolic + 5-FU weekly × 8 treatments	2-minute contact and one-time application of 5-FU solution	91.9%*	
Lawrence et al.[10] N = 15	1995	Prospective, split-face	Jessner's solution +35% TCA	Jessner's + 35% TCA	Level 1 frost	75%	12 mo
				5-FU	BID × 3 weeks	75%	
Witheiler et al.[11] N = 15 (analysis was done in 8)	1997	Prospective, split-face	Jessner's solution +35% TCA	Jessner's + 35% TCA	Level 1 frost	78%*	32 mo
				5-FU	BID × 3 weeks	79%*	
Holzer et al.[12] N = 28	2016	Randomized prospective	35% TCA	TCA	Level 1 frost	48 ± 35%*	12 mo
				ALA PDT	4-hour incubation with Tegaderm followed by red-light PDT	73 ± 29%*	
Hantash et al.[8] N = 27	2006	Randomized prospective	30% TCA	5-FU	BID × 3 weeks	83 ± 12.5%*	3 months (AKs)
				TCA	Level 2 frost	89 ± 6.6%*	5 years (keratinocyte carcinomas)
				CO2	2 passes, first pass at 6W and second pass at 5W	92 ± 10.3%*	

* $p < 0.05$.

under occlusion for 4 hours and then irradiated with blue light photodynamic therapy (PDT) with a dose of 75 J/cm^2 at an irradiance of 75 mW/cm^2. Patients were reassessed at months 1, 3, 6, and 12. If more than 50% of baseline count of AKs were present at any follow-up visit, patients were retreated with PDT. Five patients who were treated with TCA required additional treatments with PDT, whereas 2 patients treated with PDT received additional PDT treatments.

Efficacy

30% TCA peels are associated with comparable reduction in AKs relative to carbon dioxide laser resurfacing and 5-FU.[8] Combination Jessner's and 35% TCA solution demonstrates an additional benefit in reduction of histologic atypia.[10,11] When compared with ALA-PDT, 35% TCA showed lesser reduction of AKs; however, the 35% TCA peel was applied to a more superficial frost (Level 1) compared with the 30% TCA peel (Level 2).[8,12]

Adverse Effects

Overall, chemical peels are well tolerated: One study showed no side effects, such as postinflammatory hyperpigmentation or scarring, after chemical peels,[8] whereas others reported transient erythema and discomfort after application.[9,10] By contrast, 2 patients aborted laser treatment because of intolerance of the procedure.[8] 5-FU as monotherapy was associated with pain, pruritus, inflammation, erythema, and, often, erosions.[8,10,11] Combination treatment 5-FU with chemical peels such as glycolic and Jessner's peels, however, may minimize these typical side effects of 5-FU when used before a 5-FU treatment course.[9,13] Subjectively, studies reported that patients preferred chemical peel resurfacing to 5-FU because of its single application, fewer adverse effects, and rapid healing time.[8,10]

When compared with chemical peels, one study reported that PDT treatment was associated with comparatively greater pain, persistent erythema, and pustular reaction.[12] The same study also reported scarring in 6 patients (21% of enrolled patients) treated with 35% TCA.[12] Of the 6 patients with reported scarring, Holzer and colleagues[12] graded overall cosmetic outcome as excellent or good, with mild to moderate erythema or change in pigmentation, in all but 2 patients. Cosmetic outcomes that were graded as fair or poor were defined by the presence of slight to moderate or extensive scarring, respectively. Although 6 patients were reported to have scarring, there is discordance between the reported scarring and the overall graded cosmetic outcome. Limited information was provided in the study regarding other possible contributors to scarring such as infection or exogenous trauma. Moreover, additional PDT treatments for patients who had initially received a TCA peel could have potentially contributed to less favorable cosmetic outcomes.

Despite variation in adverse effects observed, the studies with mild or no side effects observed also demonstrated improved clearance of AKs compared with the one study with reported scarring.[8–12]

Prevention of Additional Actinic Keratoses

Although many lesion-directed and field treatments effectively treat AKs, field treatments have demonstrated variable effectiveness in prophylaxis against recurrent AKs or new AK development.[14] Combination Jessner's with 35% TCA peel demonstrated reduction in AK recurrence between 12 and 32 months after one treatment.[11] Witheiler and colleagues[11] observed that AK counts increased after 32 months; however, background atypia and dysmaturation remained improved after 32 months.

Prevention of Keratinocyte Carcinomas

Chemical peels may have an effect on long-term keratinocyte carcinoma prevention. At 5-year follow-up, the rate of keratinocyte carcinoma development in patients treated with TCA peels was 3.75 to 5.25 times lower compared with 5-FU and carbon dioxide laser resurfacing. One SCC in situ occurred in the TCA arm, compared with 5 SCCs and 3 BCCs in the 5-FU and carbon dioxide laser resurfacing arm, respectively.[8] Although limited by the small sample size, the TCA peel arm showed a statistically significant 40-fold decrease in the rate of keratinocyte carcinoma development compared with the control group.[8] Of the 4 treatment arms studied, the patients within the TCA group had higher AK counts and oldest age compared with the other treatment arms.[8] Overall, the demographic differences between the treatment arms in this study did not meet statistical significance.[8] These results are similar to a split-faced study that showed development of one SCC after treatment with combination Jessner's and TCA, whereas 2 SCCs developed after treatment with 5-FU.[11]

Discussion

Because of their high prevalence, potential for malignant transformation, and substantial economic burden, AKs present a major health care concern. In 2015, more than 35.6 million AK lesions were treated, compared with 29.7 million lesions treated in 2007.[13] A review of Veterans Health Administration data in 2012 showed greater than $200 million expenditure in treatment of AKs and greater than $356 million expenditure on treatment of both keratinocyte carcinomas and AKs.[14] Chemical peels are an effective, safe, and well-tolerated therapy for field treatment of AKs. Furthermore, field treatment of AKs in high-risk patients with chemical peels may prevent keratinocyte carcinomas.

Although targeted treatment of solitary AKs can be accomplished easily with cryotherapy, field treatment of AKs uses a variety of modalities. Of 5 randomized prospective studies, 4 demonstrate the significant efficacy of chemical peels in reducing the AK count.[8–11] Chemical peels have demonstrated potential for chemoprevention of future AKs and keratinocyte carcinomas while also providing cosmetic improvement.[8,11] The most well-studied peels with reduction in the AK count appear to be 30% TCA peel and the combined Jessner's solution and 35% TCA peels. From a provider perspective, chemical peels are cost-

effective by allowing treatment of large surface areas quickly with low overhead cost. The materials for a chemical peel are relatively inexpensive when compared with 5-FU or a laser.

From patients' perspectives, chemical peels were preferred to 5-FU because of single application, decreased downtime, and minimal adverse effects.[8,10] In each study, the chemical peel was applied during a single office visit. By contrast, treatment of AKs with 5-FU require full adherence to once to twice daily usage for multiple weeks. Although some studies reported patient withdrawal or severe adverse effects to carbon dioxide laser resurfacing or PDT, patients treated with chemical peels reported mild erythema and discomfort.[8–12] One study noted potential scarring after 35% TCA peel; however, some of these patients required at least one additional PDT treatment 1 to 6 months after TCA peel because of treatment failure.[12]

From a clinical standpoint, the authors recommend the following "pearls" to optimize the results of chemical peeling for field precancerization. Notably, medium depth chemical peels should not be performed off the face and scalp because of the risk of scar.[15] Before the procedure, patients should apply a retinoid cream (such as tretinoin 0.05% cream) to the affected areas nightly for approximately 4 weeks to enable even penetration of the peeling solution. During the roughly 7-day recovery, regular application of bland emollient as well as oral antiviral (such as acyclovir) prophylaxis will minimize the risk of postprocedure complications. In one author's experience (S.L.S.), organ transplant recipients on systemic retinoids for chemoprevention of AK, such as acitretin or isotretinoin, do not require prepeel topical retinization to promote efficient and even frost formation. Anecdotally, chemical peels when used as field therapy seem to offer comparable outcomes among immunocompetent and immunosuppressed patients. Another author (P.R.) uses lesion-targeted therapy with spot application of Hetter formula phenol 33%–croton oil 0.35% to flat AKs, sometimes in combination with gentle curettage to hyperkeratotic lesions, in patients who are intolerant to cryotherapy. These real-world clinical experiences may be helpful in informing the use of chemical peels in the management of AKs.

Our review is limited by the overall small number of prospective studies with relatively small sample sizes. Owing to the heterogeneity of peeling agents used, a meta-analysis based on the data from the systematic review was unfeasible. The small number of included studies is partially due to the lack of studies that performed AK counts before and after treatments. Moreover, although chemical peels are a known indication for treatment of AKs,[15] chemical peels may not be commonly used for field treatment of AKs. A survey of Australian dermatologists reported the most common indications for chemical peeling in their practices were photoaging (87%), comedonal acne (67%), lentigines (60%), and melasma (60%).[16] Although most dermatology residents receive didactic instruction on cosmetic dermatology, 46% of surveyed residents reported receiving hands-on training or lectures on chemical peels.[17] The comparatively decreased usage of chemical peels for treatment of AKs along with the overall lack of residency training on the use of chemicals peels may further contribute to the lack of available literature regarding this topic.

Conclusion

Chemical peels are a well-established and well-tolerated option for field treatment of AKs. Overall, chemical peels were better tolerated than other field treatment options, with similar efficacy and improved patient adherence. Its cost-effectiveness, potential to prevent future keratinocyte carcinoma, and acceptable side effect profile position chemical peeling as an attractive option for dermatologists and for their patients.

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