 ORIGINAL ARTICLE

Clinical Experience With 40% Hydrogen Peroxide Topical Solution for the Treatment of Seborrheic Keratosis

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ABSTRACT

Despite reassurances about the benign nature of seborrheic keratoses (SKs), patients often request treatment due to cosmetic concerns or for symptomatic relief when SKs become irritated or pruritic. Treatment options include cryotherapy, surgical techniques, and topical therapies. In this study, we present two patients with SKs located on their face and neck who received in-office treatment with 40% Hydrogen Peroxide Topical Solution (Eskata™, HP40), a new FDA-approved topical therapy that has demonstrated efficacy in phase 3 trials. Compared to non-topical, more invasive techniques, HP40 may lead to less pigmentary changes, and may be more efficacious for SKs on the face and neck. Both patients received two treatment courses of HP40, which resulted in positive therapeutic outcomes, including the absence of scarring and pigmentary changes. In addition to the case presentations, we will discuss considerations for appropriate administration of HP40 to maximize clinical outcomes.

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INTRODUCTION

As one of the most common benign lesions, over 83 million Americans are estimated to be affected by seborrheic keratoses (SKs).[1,2] The prevalence of SKs increases with age – nearly 100% of patients over 50 years old have SKs, with the average number per patient ranging from 9 to 23.[3,4] Excluding the palms, soles, and mucous membranes, SKs can occur anywhere on the body.[5] These benign epithelial tumors present as round to oval, sharply demarcated papules or plaques that appear "stuck on."[6]

Despite being prevalent, the pathogenesis of SKs is not fully elucidated. Investigation of the molecular mechanisms identified at least two mutations, in fibroblast growth factor receptor 3[7] and the oncogenic phosphoinositide 3-kinase pathway,[8] that may influence the development of SKs. Additionally, increased cyclin-dependent kinase inhibitor p16 and anti-apoptotic bcl-2 may mediate inhibition of apoptosis in seborrheic keratinocytes.[9,10] The human papillomavirus (HPV) has also been proposed to influence the formation of SKs given one study found HPV DNA in 76% of non-genital SKs, but the authors were skeptical about HPV being a true causative factor given multiple HPV types were found in one specimen.[11] Further, HPV can be found in normal skin.[10] Similar to the pathogenesis, the etiologic risk factors for SKs are not completely understood. Increasing age is a known risk factor as demonstrated by numerous prevalence studies.[3,4] Ultraviolet light exposure may also increase the risk of SKs, but the evidence is conflicting with two studies showing that SKs are associated with sun exposure,[3,4] but another study finding that they are not.[12] Finally, friction may contribute to the development of SKs as they often occur in intertriginous areas.[5]

Patients often desire treatment for SKs out of concern that the skin finding is something serious, for cosmetic reasons, or for symptomatic relief as they can become irritated, painful, or pruritic.[5,13] SKs are typically diagnosed clinically, but histologic confirmation is recommended for atypical, inflamed, or changing lesions.[6] In these cases, a shave excision should be done to preserve tissue for diagnosis.[5] Table 1 presents the current treatment options for SKs, including cryotherapy, surgical techniques, and topical therapies. Cryotherapy is the most common treatment,[5] however, this therapy and the surgical techniques presented in Table 1 can lead to pigmentary changes, especially in patients with Fitzpatrick Skin Type IV-VI.[5] Cryotherapy and surgical techniques can also cause bleeding, pruritus, or scarring.[5,14–21] To avoid these adverse effects, various topical therapies have been utilized to treat SKs (Table 1). The efficacies of keratolytics including ammonium lactate, imiquimod, and tazarotene have been examined but overall, these therapies had limited success in small clinical trials.[2,22,23] Topical vitamin D analogs have also been used, but similarly, these had limited efficacy for treating SKs.[2,24] Given the inadequacy of existing topical therapies, safe and effective non-invasive therapies are still needed. One novel therapy is BL-5010, a combination of trichloroacetic acid and formic acid. In a phase I/II open-label trial, a single treatment with BL-5010 resulted in a complete response in 90% of patients and partial response in 7% of patients six months after application (n=60).[25] The medication was well-tol-

TABLE 1.

Surgical Therapies		
Type	**Description and Outcomes**	**Side Effects**
Liquid nitrogen cryotherapy	• Destroys SKs by forming ice crystals that damage cells and via an inflammatory mechanism that is not fully elucidated.[28,32] • Useful for thin, small SKs in non-cosmetically sensitive areas; can be combined with other therapies for thicker SKs.[5] • Success depends on SK thickness, freezing time, and number of freeze/thaw cycles;[2,14,15] >1 treatment may be needed for clearance.[5] • Clinical and histologic clearance was seen in 15/15 patients in one trial.[2] In another trial, residual disease was more common with cryotherapy than curettage, but patients preferred cryotherapy given less wound care was required.[16]	Pain, burning, bleeding, blistering, scarring, or pigmentary changes, including post-inflammatory hyperpigmentation and permanent depigmentation from melanocyte destruction.[5,17]
Electrocautery	• Destroys SKs via electrodessication (electrode applied to skin) or electrofulguration (electrode held near skin).[5] • Useful for small lesions in patients with dark skin (may have a lower risk of pigmentary changes than cryotherapy).[5]	Pain, pigmentary changes, or scarring.[18]
Curettage	• Useful alone for small, thin lesions or in combination with electrocautery or cryotherapy for thicker lesions. • Requires post-procedure wound care.[16]	Pain (less than with cryotherapy); scarring or hypopigmentation (higher risk than cryotherapy).[16]
Shave excision	• Allows for rapid removal of a single SK and preserves tissue for diagnosis.[5] • Requires local anesthesia and wound care after the procedure, but has acceptable cosmetic outcomes with proper post-procedure care.[5]	Pain, pruritus, bleeding, infection, or scarring.[19]
Laser therapy	• Ablative and non-ablative lasers have been used to destroy SKs.[14] • Useful for large surface areas or multiple SKs.[14,15] • 755-nm alexandrite laser was used to treat hundreds of SKs in one patient with a good cosmetic outcome[15] and in a small study (n=13) where it resulted in complete resolution of SKs.[20] • 532-nm diode laser cleared 96% of SKs in one study (n=326).[21]	Pain, scarring, or pigmentary changes (lower risk with non-ablative lasers than ablative lasers).[14,15,20,21]
Topical Therapies		
Type	**Description and Outcomes**	**Side Effects**
40% H2O2	• Mechanism likely involves the oxidizing effects of H2O2.[26] • FDA-approved to treat raised SKs, but not covered by insurance.[26] • Less cytotoxic to melanocytes than cryotherapy in an ex vivo model,[31] so it may be useful to treat SKs in cosmetically-sensitive areas. • >1 treatment may be needed for clearance.[26]	Burning, scaling/crusting, erythema, pruritus, erosions, pigmentary changes, or scarring.[26]
BL-5010	• Combination of trichloroacetic acid and formic acid.[25] • Proposed mechanism: in situ cell fixation leads to cell death and detachment of SKs.[25] • Phase I/II open-label trial: single application (n=60) resulted in SK detachment in 97% of patients 30 days later. Six months later, 90% experienced a complete response and 7% a partial response. Treatment was well-tolerated overall.[25]	Burning, pruritus, bleeding, scaling/crusting, erythema, or edema.[25]
Vitamin D analogs	• Affects differentiation and apoptosis of keratinocytes.[2,33] • Various ointments were applied 1-2 times/day for 3-12 months (n=116); only 30.2% of patients experienced 80-100% decrease in volume.[24] In another trial (n=15), 0.005% calcipotriene ointment did not produce any clinical improvement.[2]	Erythema, burning, or irritation have been reported, but no side effects occurred in the trials.[2,24]
0.1% Tazarotene cream	• Binds retinoic acid receptors in keratinocytes leading to anti-proliferative effects.[2] • Twice daily use resulted in clinical and histologic clearance in 7/15 patients (compared to 15/15 with cryotherapy).[2]	Burning, pruritus, or erythema (but tolerance to side effects develops with continued use).[2]
Imiquimod 5% cream	• Immune response modulator that is effective for other skin neoplasms.[2,6] • Did not result in clinical improvement in one trial (n=15),[2] but was successful for one patient with SKs positive for multiple HPV types.[22] Therefore, it may only be effective for SKs with HPV DNA.[6]	Erythema, burning, or ulceration (can persist for >1 month).[2]
12% Ammonium lactate	• Keratolytic that decreased SK height compared to vehicle but did not affect SK length, surface characteristics, and color; only cleared two SKs after 16 weeks of twice daily use (n=58).[23]	Burning or erythema.[34]

erated but the authors did not discuss the risks of pigmentary changes or scarring. Larger studies are needed to further examine BL-5010's safety and efficacy. Another new therapy is a stabilized, high concentration hydrogen peroxide (40% H2O2) solution (Eskata™, HP40), which is the first FDA-approved topical therapy for raised SKs.[26]

HP40 is applied topically with a single-use, disposable applicator pen that can be used to treat multiple SKs in one setting (up to 10 if the SKs are small based on the author's experience). Per the manufacturer's protocol, the H2O2 solution is rubbed onto each SK in a circular motion to uniformly coat the surface. This process is repeated three additional times for each SK, separating each application by approximately one minute. After three weeks, another treatment may be needed if the SKs do not completely disappear. The efficacy of HP40 for the treatment of four SKs per patient was examined in two Phase 3 trials (n=937). Compared to vehicle, 1-2 applications of HP40 resulted in a higher mean per-patient percentage of clear/nearly clear SKs (51% for HP40 versus 7% for vehicle).[26] A further sub-analysis showed that the percentage of clear/nearly clear SKs was higher for the face (65%) than for other locations (46% for trunk, 38% for extremities).[27]

In this case series, we present two patients who received in-office treatment with HP40 for SKs located on their face and neck. This novel topical therapy resulted in positive therapeutic outcomes for both patients presented. Further, we will discuss practical considerations for using HP40 based on the author's experience with this product.

CASE 1

A 52-year-old Caucasian female with Fitzpatrick Skin Type II presented for treatment of numerous SKs on her face and neck. A few years ago, she received treatment for SKs located on her neck with cryotherapy, but she was disappointed with the hypopigmented scars left behind. The patient was deemed to be a good candidate for HP40 treatment given she had a previous negative experience with cryotherapy and had multiple lesions in cosmetically-sensitive areas. A total of 9 SKs on her face, hairline, and neck measuring from 5 mm to 1.2 cm (Figure 1A) were treated with one HP40 pen according to the product's protocol (Figure 1B). The patient was evaluated 20 days later and given the presence of residual disease (Figure 1C), all 9 SKs were re-treated following the same procedure. The patient was seen again 106 days after the initial treatment; complete resolution of all the SKs was appreciated on exam (Figure 1D) and the patient was happy with the outcome.

CASE 2

A 37-year-old Hispanic male (Fitzpatrick Skin Type IV) presented for treatment of several dark, painless lesions on his face that were bothersome in appearance and grew slowly over the past several years. On exam, the patient had multiple well-defined, brown, raised papules measuring 4 mm to 8 mm on the right side of his face, consistent with SKs (Figure 2A). Considering the location of the SKs and the patient's skin type and age, topical treatment with HP40 was recommended. The SKs were

FIGURE 1. SKs on the face and neck, Case 1. (1A) Before first HP40 treatment. (1B) Immediately after first HP40 treatment. (1C) 20 days after first HP40 treatment. (1D) Final result, 106 days after first HP40 treatment/86 days after second HP40 treatment.

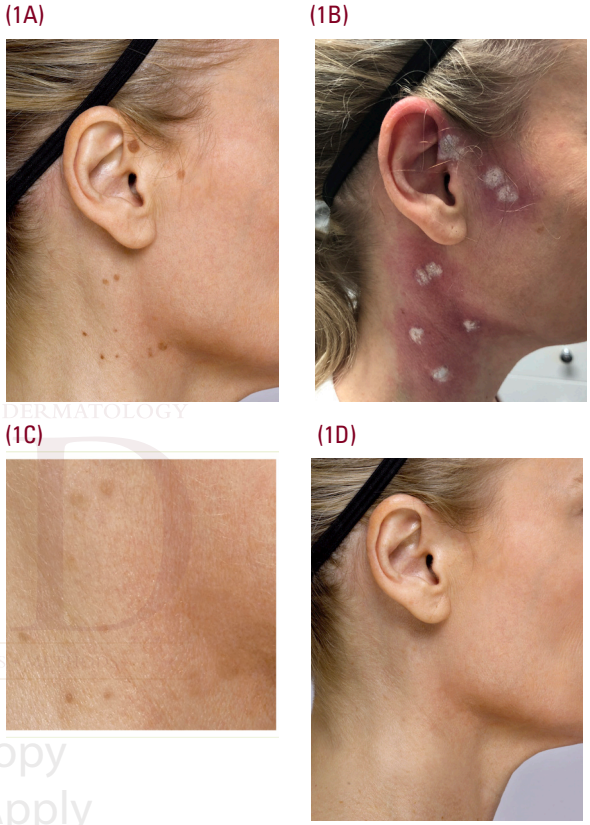
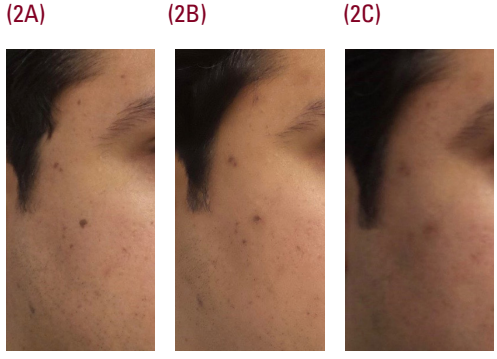


FIGURE 2. SKs on the face, Case 2. (2A) Before first HP40 treatment. (2B) 42 days after first HP40 treatment. (2C) Final result, 70 days after first HP40 treatment/28 days after second HP40 treatment.



treated with one HP40 pen according to the manufacturer's protocol. At a follow-up visit six weeks later (Figure 2B), residual disease was present, so all the SKs were retreated with HP40. Four weeks later (70 days after the first treatment), the SKs were nearly clear without scarring, an outcome that pleased the patient (Figure 2C).

DISCUSSION

HP40 was recently FDA-approved to treat raised SKs and as demonstrated by the two cases presented here, this in-office treatment can lead to positive therapeutic outcomes for SKs located in cosmetically-sensitive areas. The mechanism by which HP40 destroys SKs is not fully understood, but it likely utilizes the oxidizing potential of H2O2.[28] H2O2 can directly damage cell components as a reactive oxygen species and form hydroxyl free radicals to exert further oxidative damage.[29] Applied at supraphysiologic doses, HP40 delivers a fraction of the dose through the stratum corneum (SC) to the epidermis, where it can generate free radicals by overcoming the skin's antioxidant capabilities and initiate cellular apoptosis and necrosis. Because of this mechanism, HP40 should not be applied to open or infected SKs where the SC is compromised. The SC protects deep tissue from high concentration H2O2 so without this barrier, H2O2 can cause rapid death of nearby cells.[30] However, when used properly in phase 3 trials, side effects of HP40 were limited to local skin reactions, the majority being mild to moderate.[26] Scarring, hypopigmentation, and hyperpigmentation occurred in less than 1%, 3.0%, and 7.8% of sites treated with HP40, respectively.[26] Although, nearly all of the participants were Fitzpatrick Skin Types I to IV, so the effect of HP40 on darker skin is less clear.[26] In an ex vivo model of human Fitzpatrick Skin Type V, HP40 was less toxic to melanocytes compared to cryotherapy.[31] Therefore, HP40 may be superior to cryotherapy for skin of color, but large, controlled studies including multiple skin types are needed to compare these therapies.

In support of HP40's potential to minimize the risk of scarring and pigmentary changes, the patient in Case 1 was previously treated with cryotherapy, which led to hypopigmented scarring. However, as seen in Figure 1D, there was no evidence of scarring or hypopigmentation from HP40 after over three months. The patient in Case 2 with Fitzpatrick Skin Type IV was similarly spared of these adverse effects. While HP40 still has a small risk of scarring and pigmentary changes, this is a good option to discuss with patients who want to minimize the side effects from treating SKs in visible skin areas.

Selecting a therapeutic strategy for SK removal requires consideration of the location of SKs as well as the patient's skin type and expectations of what will be left behind after removal. Given HP40 is not covered by insurance and multiple treatments may be needed, patients with SKs in non-cosmetically sensitive areas may prefer treatment with cryotherapy, curettage, or electrodessication. However, patients with SKs in cosmetically-sensitive areas like the face and neck, particularly those with dark skin types, may benefit from a topical therapy like HP40 that is less cytotoxic to melanocytes and the neighboring epidermis.[31] This is especially true if patients are dissatisfied with previous treatments. Further, as demonstrated by phase 3 trials[26] and based on the author's experience, raised SKs on the face and neck respond especially well to treatment with HP40.

In addition to instructions provided by the manufacturer, the following practical considerations based on the author's experience may be helpful when using HP40. It is important to apply firm pressure and cover the entire lesion, while staying within a 2 to 3 millimeter margin of the SK to avoid contact with normal skin. Four treatment cycles are recommended for each SK, but if the patient experiences 6 to 7 or more pain on a scale of 0 to 10, the treatment should be terminated. Additionally, when treating SKs near the orbital rim, some eyelid swelling is expected; reassure the patient that this usually resolves in a few hours.

Overall, HP40 is a new therapeutic option for SKs that can be discussed with patients. As demonstrated by the cases presented here, HP40 is particularly useful for SKs on the face and neck and may avoid the scarring and hypopigmentation that can occur with cryotherapy. Future examination of HP40 in patients with dark skin types is needed to confirm our suspicion that HP40 may lead to less pigmentary changes than non-topical, invasive therapies.

DISCLOSURE

The authors have no conflicts of interest.

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