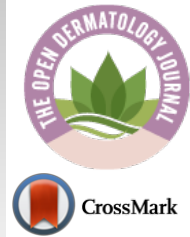




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REVIEW ARTICLE

Hydrogen Peroxide Use for Chemical Destruction in Seborrheic Keratosis: A Review

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Abstract:

Seborrheic Keratosis (SK) is a common, benign epidermal tumor as observed by dermatologists. Removal is rarely indicated, and usually requested by patients for cosmetic preference. The most common method of removal is cryotherapy, but other topical treatments exist. Topical Hydrogen Peroxide has been recognized as an effective topical treatment. Safety concerns and maximum efficiency of peroxides have been a topic of study in a variety of dermatological conditions. This article aims to review the chemical composition of hydrogen peroxide (H₂O₂) in treating SK, methods to increase its effectiveness as a topical dermatological product, and explore the promising new FDA approved treatment.

Keywords: Hydrogen peroxide , Seborrheic keratosis , Cryotherapy, Topical hydrogen peroxide, Epidermal tumor, FDA.

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1. INTRODUCTION

Seborrheic Keratoses (SK) are common, benign tumors of the epidermis that first appear most often in middle-aged men and women. They can occur on any part of the body except for the palms and soles but often present on sun-exposed areas such as the face and forehead. SK are well demarcated gray-brown to black lesions, which can be raised and covered with greasy scales [1, 4]. They are benign neoplasms characterized by the accumulation of epidermal keratinocytes arrested in the G1 phase of the cell cycle, in cellular senescence. Expression of a cyclin-dependent kinase inhibitor, p16 is implicated in its pathogenesis [5]. Somatic mutations have also been implicated in SK pathogenesis, such as FGFR3, in which increasing age and ultraviolet light exposure increase the risk for development [1].

SK can be divided into six histopathological categories: acanthotic, hyperkeratotic, adenoid, irritated, clonal and melanoacanthoma. Regardless of the subtype, all SK lesions display hyperkeratosis, acanthosis and papillomatosis [3, 4]. A study completed by Roh *et al.* concluded that the acanthotic subtype was the most prevalent among skin biopsies, with the adenoid type occurring most commonly on sun-exposed sites. Variations in the presentation of SK do exist, with the greatest concerns occurring with lesions that mimic premalignant or malignant epidermal tumors. Acanthotic SK [4] can resemble Bowen's disease, while SK with basal clear cells can look like melanoma *in situ* [2]. The Leser-Trélat sign

is defined as an increase in the number and size of seborrheic keratoses, and is considered a paraneoplastic syndrome most commonly associated with GI tract adenocarcinomas or lymphoproliferative disorders [1].

Thus, if lesions undergo any sudden changes in size, shape or number, and acute symptoms arise in the patient, concern for pre-malignancy is high and removal is indicated. Other reasons for removal include SKs presenting as pruritic, irritating or erythematous. In most cases, lesions are benign and removal is not indicated unless requested by the patient for cosmetic reasons. A survey completed by Jackson *et al.* demonstrated that on average, dermatologists treat 43% of their patients' SK lesions, with cryosurgery being the most common method of removal. Other common methods include shave excision, electro-dessication, topical treatment, or curettage [6].

1.1. Current Topical Treatments for Seborrheic Keratosis

A common method of Seborrheic Keratosis removal is cryotherapy. In a pilot study completed by Wood *et al.*, 60% of patients included in the study preferred cryotherapy as opposed to curettage citing decreased wound care with cryotherapy [7]. Certain topical treatments have also proven useful, although the literature on this topic remains limited. A study completed by Burkhart and Burkhart revealed that the use of topical 50% urea containing the product applied daily to hyperkeratotic SKs with scraping resulted in reasonable patient satisfaction [8]. Topical 0.1% Tazarotene cream with a twice a day application caused clinical and histological improvement in a small study done in seven of 15 patients, with the application site being indistinguishable from normal skin [9] Vitamin D analogs have

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also proven effective in treating lesions of SK. Vitamin D is present in the epidermis and deficiency has been linked to excessive proliferation of cells in the skin. A clinical study of 116 patients found that approximately 30.2% of patients observed complete disappearance with 80% seeing a reduction in the volume of their SK lesions over time [10].

1.2. Maximizing Efficacy of Peroxides in Treatment of Seborrheic Keratosis

Topical treatment with peroxides, including benzoyl peroxide and hydrogen peroxide has been identified as efficient treatments in a variety of dermatological conditions. Various studies have been conducted that test the efficacy and safety of these treatments to determine conditions in which they offer clinical benefit. The exact mechanism by which hydrogen peroxide treats seborrheic keratoses is unknown. However, topical treatment is thought to result in dissociation of the chemical into water and Reactive Oxygen Species (ROS), which results in skin cell death [11].

The location and timing of the formation of radicals are very important in its therapeutic effects. A more effective peroxide product to treat SK could be formulated by using an instrument that agitates or stirs the peroxide with stimulators, such as tertiary amines or trace metals prior to topical application. Using tertiary amines as activators of peroxides increases the production of ROS, while trace metals stabilize the transition state and act as catalysts to reduce the energy required for the formation of ROS. In turn, these chemicals in concert boost the biological utility of peroxides. The reaction between the activators and BP is fast, so the maximum biological effect can be obtained by keeping these chemicals separate until just before contacting the skin surface [12,13].

Using a high concentration of the peroxide in a small location of skin could also maximize its effectiveness and minimize the harm done to the rest of the normal skin. This could be accomplished by using a pen-tip applicator for SK and agitating the liquid prior to application. However, high concentrations of hydrogen peroxide, specifically, have been used in the production of bombs and must be handled carefully and safely. Limits must be placed on dosing; the concentration of the product being used and the amount necessary for the patient. Safety precautions include using water to neutralize the chemical, *i.e.* washing the area of skin exposed immediately after application, reducing the risk for potential side effects from peroxide usage. Additionally, antioxidant rescue in which treatment of SK with peroxides is followed by antioxidants which combat ROS to preserve normal cells can be utilized to prevent unwanted skin destruction following the use of highly concentrated hydrogen peroxide.

A more effective peroxide would also increase the interaction of the chemical with the skin itself. Peroxide efficiency is maximized if used on a base that is highly polar. One could also use some sort of surfactant on the skin, to prepare it for a more receptive environment to the ROS formed by peroxides. Surfactants are amphiphilic substances which if used correctly to prime the skin could help lipophilic peroxides penetrate deeper parts of the skin for more concentrated destruction.

The use of benzoyl peroxide with a tertiary amine in the treatment of dermatophyte and bacterial infections *in vitro* was

studied by Burkhart and Burkhart [12]. Biological synergy in antimicrobial therapy was discovered when benzoyl peroxide was used in concert with a tertiary amine such as erythromycin or clindamycin. Tertiary amines stimulate BP, initiating the one-electron transfer reaction with lower oxidation states to allow polymerization and increased biological effect [12]. In this study, terbinafine, a drug shown to be highly active against dermatophytes, is an allylamine with a chemical structure that has an accessible tertiary amine for interaction with benzoyl peroxide. A checkerboard assay was used to determine the Minimum Inhibitory Concentration (MIC) of Benzoyl Peroxide (BP) and terbinafine against various infections, including *Candida albicans*, *Pseudomonas* and *Staphylococcus*. Studies revealed combining BP with terbinafine led to synergistic effects against all *C. albicans* isolates with a lowered MIC against most other bacterial isolates with no antagonistic effects between drugs [12]. The results of this study support the enhancement of peroxide *in vitro* with activators. This could potentially be extended to *in vivo* studies to effectively treat other dermatological conditions, including seborrheic keratosis.

1.3. ESKATA: Topical 40% Hydrogen Peroxide for Seborrheic Keratosis

Eskata, developed by Aclaris Therapeutics is a 2018 FDA approved treatment for raised SK lesions. This topical treatment contains 40% concentrated hydrogen peroxide in a solution of isopropyl alcohol and water, and is a non-invasive treatment launched commercially for physician use and administration. This product is marketed as a non-invasive treatment that is painless and leaves skin without scarring or pigmentation via oxidative damage [14]. Physicians are to use nitrile or vinyl gloves while handling Eskata and SK lesions are to be wiped with an alcohol wipe prior to application. One use includes four applications of Eskata, approximately 1 minute apart. Two uses are recommended for removal of SK lesions [14].

A preliminary clinical trial of 937 patients with four target SK lesions across 34 US centers was utilized to test the effectiveness of Eskata. Out of 937 patients, 467 were administered Eskata, while the remaining were administered a placebo. The goal of this study was to calculate the percentage of patients treated with Eskata and evaluate the complete clearance of all SK lesions after treatment. The results showed that patients treated with Eskata observed total or near clearance of all SK lesions after two treatments, when compared with patients who received the placebo. 13.5% of patients treated with Eskata noted clearance of at least three of the four SK lesions, and in a follow-up study with an advanced clinical version of Eskata, the number rose to 23% of patients. Overall, combined trial results concluded that 51.3% of lesions treated with Eskata had total or near clearance compared to 7.3% of SK lesions in the placebo group. In addition, studies showed that 65.3% of lesions on the face treated with Eskata were totally or nearly cleared as opposed to 10.5% of lesions in patients receiving the placebo [14]. In terms of clinical response, the smaller the lesion in terms of size and induration, the better the response when treated with any hydrogen peroxide. In terms of healing, the face and areas with better circulation respond faster than the legs. Age is also a factor. It can take four weeks for the entire epidermis to regenerate, and it is better for patients to realize that it could take up to four weeks for full resolution of SKs after treatment. In addition,

thicker lesions may require more than one treatment.

Side effects with Eskata exist and can include adverse ophthalmic injury, and local skin reactions. These reactions consist of erythema, stinging, edema, pruritus, and vesiculation. Eventual ulceration, crusting, scaling and hyper or hypopigmentation can also persist about a month after treatment. [11].

Promising features of Eskata include a pen-like applicator, which maximizes contact with SK lesions, while minimizing the damage done to the surrounding normal skin. The high concentration of hydrogen peroxide leads to effective oxidative damage leading to the disappearance of the SK after two uses [14]. However, treatment could possibly benefit patients further if agitated and mixed with a tertiary amine to increase ROS production or if the skin was prepped in a way to make ROS destruction more efficient. Side effects could be minimized with immediate washing, or administration of an anti-oxidant after exposure. Further studies and testing of activators with Eskata could potentially lead to an even better and more effective treatment of seborrheic keratosis.

CONCLUSION

Seborrheic Keratoses are a common benign skin condition affecting older adults. It is of importance that if patients choose the removal of these lesions, treatments for SK are effective and safe. Topical concentrated hydrogen peroxide is a proven treatment for SK and a variety of dermatological conditions, which work by releasing Reactive Oxygen Species for target skin destruction. Possible methods to increase the efficiency of hydrogen peroxide as a topical treatment include creating a solution with an activator such as a tertiary amine in which the chemical release of ROS is maximized, agitating the solution before application, priming the skin surface, and managing the timing and location of the H₂ reaction with the skin such that maximal ROS release is achieved. Safety precautions include antioxidant rescue, and thorough washing of skin immediately following treatment. The new topical concentrated hydrogen peroxide treatment, Eskata, utilizes a few of these methods but has only recently been approved for use in clinical practice. Still, further improvement of this product through chemical testing and further study of the chemical interactions of hydrogen peroxide and ROS may lead to an even safer and more efficient treatment of Seborrheic Keratosis.

CONSENT FOR PUBLICATION

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CONFLICTS OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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