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REVIEW ARTICLE

Reexamination of Treatment of Seborrheic Keratosis Given Availability of New Prescription Therapy With Hydrogen Peroxide

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Abstract: Seborrheic Keratoses (SKs) are one of the most common dermatologic lesions seen by dermatologists. They are biologically benign and do not usually require removal for medical reasons; however, many patients choose removal due to cosmetic preferences. Currently, cryotherapy (liquid nitrogen spray) is the most common mode of removal [1]. Although patients often desire an effective topical treatment, few have been developed that rival the effects of cryotherapy. This article aims to review current available topical treatments, with a particular focus on both the benefits and potential pitfalls of a novel treatment, concentrated Hydrogen Peroxide (H_2O_2).

Keywords: SK, Hydrogen peroxide, Cryotherapy, Dermatologic lesions, Topical treatments, Epidermal tumor.

1. INTRODUCTION

Seborrheic Keratosis (SK) is one of the most common benign epidermal tumors seen by dermatologists. SKs affect men and women equally, and usually arise in patients over the age of 50 years old [1, 2]. SKs are composed of an accumulation of senescent epidermal cells that have been arrested in the G1 phase of the cell cycle. Apoptosis of these cells is inhibited by p16 (a cyclin-dependent kinase inhibitor) which is overexpressed in all SK lesions [3]. They typically present as well demarcated, slightly elevated patches or plaques that range in color from flesh-toned to gray, brown, or black [1, 2].

Variation in this presentation does exist, and may suggest a variety of benign or malignant lesions, or inflammatory eruptions. According to a 2014 United States Survey involving 594 practicing, board-certified dermatologists, 43% of patients with SKs decide to undergo removal of the lesions. Upon consideration for removal, it is suggested that the lesions are first categorized as of either cosmetic or medical concern [4]. Biologically benign, removal of SKs is not warranted unless histological confirmation indicates otherwise, or the lesions become pruritic, erythematic, or otherwise an irritant to the patient. Of notable concern is Leser-Trélat, a paraneoplastic sign characterized by a sudden appearance and/or increase in the number of SKs [5]. Leser-Trélat may be an indicator of stomach, ovary, uterus, or breast carcinomas, and in other rare cases an indicator of bladder, lung, or larynx carcinomas [6, 7].

Thus, if the lesions undergo any abnormal or sudden change in shape or size, inflammatory changes occur, acute symptoms arise, *etc*. then the concern for malignancy is high and removal is indicated [1]. A majority of the time, however, removal is not indicated and treatment is completed for cosmetic purposes.

2. CURRENT TOPICAL TREATMENTS

When treatment is either indicated or desired, the preferred first line of treatment is cryotherapy, using liquid

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nitrogen spray. In a pilot study of 25 people by Wood et. all, 60% of patients preferred cryotherapy to curettage when it came to the removal of their SKs [8]. However, cryotherapy is not without its downfalls: in the same study, SKs treated with cryotherapy were more likely to have leftover lesions. There is also an array of topical treatments, although the literature on most is limited and the proven efficacy of most leaves much to be desired.

Topical keratolytics are often used for SKs, although the FDA has still not approved any of these treatments [1]. The most notable and perhaps the best-documented keratolytic is 0.1% tazarotene. Tazarotene exerts its effects by targeting and binding retinoic acid receptors beta and gamma, and thus leads to a decrease in proliferation of SK cells as well as a decrease in inflammatory markers [9]. In a small study of 15 subjects, it was shown that twice-daily application of 0.1% tazarotene cream caused SKs to be indistinguishable from the normal skin at the end of 6 months of treatment. All patients who responded to this treatment determined the topical treatment to be satisfactory, and wished to continue treatment with tazarotene in the future [10]. Tazarotene cream has also proved to be relatively effective in the treatment of plaque psoriasis in clinical trials, as well as reducing lesions in patients with mild to moderate facial acne. However, it is contraindicated in patients that are pregnant or plan to become pregnant [9].

Vitamin D analogs have also been shown to have some efficacy against SKs [10, 11]. Vitamin D is present in the epidermis, and ligand-dependent Vitamin D Receptor (VDR) has been shown to play a role in keratinocyte differentiation and proliferation. VDR deficiency has been linked to a hyperproliferative response in the epidermis. Therefore, treatment with Vitamin D ligand can reverse these effects and slow proliferation [12]. During one clinical study [12], 116 patients with SKs were treated from 3-12 months with Vitamin D analogs (tacalcitol, calcipotriol, or maxacalcitol). After treatment, 30.2% of patients saw either complete disappearance or at least 80% reduction in the volume of their SKs, and 46.4% saw a reduction in volume between 40 and 80%. In a second study, however, calcipotriol did not result in clinical improvement and thus the results of using these Vitamin D analogs are not clear [10].

Another viable option for treatment of SKs is 50% urea. Urea works as a keratolytic by disrupting non-covalent interactions and partially unfolding proteins, therefore loosening the outermost layers of the SKs. Subsequent scraping of lesions may allow enough removal to show cosmetically pleasing results [13]. A pilot study of 20 subjects conducted by Burkhart & Burkhart [13] instructed patients to apply 50% urea ointment once daily and then cover it with a bandage. They were also instructed to scrape the surface of the lesion once or twice a week for 6 weeks. Patient satisfaction after this trial was rated on a scale of 1-10. The survey was significant for reduction in the lesion's thickness, which was rated 7.4 /10 upon completion of the trial. Also of note, patients rated their desire to continue using the topical product as an 8.3/10 [13].

Benzoyl peroxide in combination with a tertiary amine is another treatment for SK that has limited reports on its efficacy, although topical benzoyl peroxide has historically been an effective treatment for acne [14]. Tertiary amines have previously been shown to increase the radical formation of benzoyl peroxide, and therefore make it more effective as a topical treatment [14]. In a small study conducted by Burkhart [15], 8 patients with SKs greater in size than 2 cm and 0.3 cm in thickness were treated with benzoyl peroxide daily in addition to topical terbinafine (containing a tertiary amine), and then instructed to cover the lesion with a bandage. Four months into this treatment, none of the patients showed complete clearance of their lesion, but there was a reduction in the size of their SKs. The biggest change was a 50% reduction in size [15]. While this study showed variable results, the large size of the SKs may have hindered success in such a short amount of time. More studies on benzoyl peroxide in combination with a tertiary amine are needed before judgment is made on the efficacy of this treatment [15].

3. TOPICAL CONCENTRATED HYDROGEN PEROXIDE

Highly concentrated Hydrogen Peroxide (H_2O_2) has recently been indicated as a feasible treatment for SK. Hydrogen peroxide is a highly reactive species, and even localized concentrations must be carefully controlled. The oxidizing power of H_2O_2 can generate reactive oxygen species (ROS) that directly damage the mutated SK cells, ultimately resulting in apoptosis and necrosis of the SK [16]. Clearly, the danger in this method is having the ability to carefully and precisely control the ROS in order to minimize damage to healthy, normal skin around the abnormal lesions. Currently, the most common concentrations of H_2O_2 available to the public are 3% and 30% [17]. It is possible to purchase these concentrations of H_2O_2 on websites such as e-bay and Amazon. A major concern is that if 35-40% H_2O_2 becomes a common-place treatment for SKs, non-physicians may try to self-medicate in order to save time or money by using similar concentrations available for purchase online. Untrained individuals using topical concentrated hydrogen peroxide could result in irreparable damage.

In a multicenter, double-blind, study by DuBois *et al.* [16], 119 subjects were placed into three treatment groups: A-101 40% solution, A-101 32.5% solution, or vehicle solution (control). A-101 is a topical, highly concentrated solution of H_2O_2. The solutions were applied to the target lesion (in this particular study, all lesions were on the face) at Days 1 and 22 of the study, unless a second treatment was contraindicated. Three scales were used to determine the efficacy of the solutions: Physician's Lesion Assessment (PLA), Subject's Self Assessment (SSA), and Local Skin Reaction (LSR) Assessment. On day 106, patients' lesions were measured and graded appropriately. Results showed a mean reduction in PLA by 1.7 for A-101 40%, 1.4 for A-101 32.5%, and 0.1 for the vehicle alone. In addition, 68%, 62%, and 5% of subjects, respectively, had lesions that were judged as "clear" or "near clear" on Day 106 [16].

Concentrated liquid hydrogen peroxide is not widely used at the moment, and for good reason. In a law enforcement training article [18], it is described how liquid bombs can be made from concentrated H_2O_2 in combination with acetone or ethanol, and even less conspicuous compounds such as black pepper or sugary drink powders [18]. This method has been used in several terrorist attacks, most notably the attack on the London transit system in 2005. In 2006, liquid concentrated hydrogen peroxide bombs were created with the intention of blowing up several airplanes, but this attack was stopped [18].

Solid hydrogen peroxide bombs can also be created from a liquid concentrated hydrogen peroxide base. Solid hydrogen peroxide bombs are much more unstable and dangerous to handle than their liquid counterpart [18]. They have also been used in a variety of attempted attacks, including one solid hydrogen peroxide bomb that detonated early outside of a University of Oklahoma football game in 2005, killing the student carrying it [18].

In addition, concentrated hydrogen peroxide has recently been utilized as a new way to produce rocket propellant [17]. However, the H_2O_2 used for fuel must be concentrated to 90% or higher to eliminate deleterious side effects such as decomposition upon contact with various surfaces. This highly concentrated hydrogen peroxide is made in three steps: isopropyl alcohol autoxidation, hydrogen peroxide extraction, and acetone extraction. In addition to these main three steps, there are concurrent steps that lead to the explosive nature of H_2O_2, so this process must be very carefully controlled [19].

Taking all of this into consideration, while concentrated hydrogen peroxide may at first brush seem like an easy and reasonable topical fix for SKs, much more thought must go into employing proper safety measures before the topical is released in prescription form or even widely used by physicians. Even a small amount of this solution ending up in the wrong hands or non-physicians hoping to self medicate could have tragic repercussions.

CONCLUSION

Seborrheic Keratosis (SK) is one of the most common lesions in older patients, and dermatologists are particularly skilled at diagnosing and treating them. SKs do not normally need to be removed for biological reasons, but they should be monitored closely for any changes that may suggest malignancy. Topical treatments for SKs have historically varied in their efficacy and desirable results. There are still no FDA approved topical treatments, although many have been used with a spectrum of outcomes. Recently, concentrated hydrogen peroxide has been proven to be a fierce competitor in the race to find a topical treatment for SKs. Of notable concern, however, is the use of concentrated hydrogen peroxide to make liquid bombs, solid bombs, and rocket propellant. This treatment still has a long way to go in order to be deemed safe and effective for all to use, but hopefully, subsequent studies will continue to produce evidence that H_2O_2 can be an effective first-line treatment for SK.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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