Hydrogen peroxide and cutaneous biology: Translational applications, benefits, and risks

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Hydrogen peroxide (H_2O_2) is an endogenous reactive oxygen species that contributes to oxidative stress directly as a molecular oxidant and indirectly through free radical generation. Topically applied 1% to 45% H_2O_2 can be used for a range of clinical purposes, which will be reviewed here in addition to its safety. In concentrations from 1% to 6%, H_2O_2 has antimicrobial properties and can act as a debriding agent through its effervescence, making low-concentration H_2O_2 useful for wound care. H_2O_2 has also been shown to promote venous insufficiency ulcer healing, but studies in other wound types are needed. In 1% formulations, H_2O_2 is used outside the United States to treat acne and has shown efficacy similar to or greater than benzoyl peroxide, with reduced side effects. In a concentration of 40%, H_2O_2 is US Food and Drug Administration–approved to treat seborrheic keratoses and may cause fewer pigmentary changes than cryotherapy, although elimination often requires 2 to 4 treatments. However, H_2O_2 should be used with caution, as exposure can cause adverse effects through its oxidant capabilities. Low H_2O_2 concentrations cause only transient symptoms (blanching and blistering), but exposure to 9% to 45% H_2O_2 can cause more severe skin damage, including epidermal necrosis leading to erythema and bullae. Overall, H_2O_2 has numerous therapeutic uses, and novel indications, such as treating actinic keratoses and skin cancers, continue to be explored. (J Am Acad Dermatol 2019;81:1379-86.)

Key words: actinic keratosis; antiseptic; free radicals; hydrogen peroxide; reactive oxygen species; seborrheic keratosis; skin cancer; Warburg effect; wound healing.

Hydrogen peroxide (H_2O_2) is a reactive oxygen species (ROS) that can oxidatively damage lipids, proteins, and nucleic acids, either directly or indirectly through the formation of hydroxyl radicals ($OH^{\bullet}$) and downstream propagation of additional ROS.[1] Endogenous H_2O_2 can be formed by cellular enzymatic reactions or the spontaneous dismutation of superoxide (O_2^-) (Fig 1).[1] In contrast to O_2^-, H_2O_2 can diffuse across cell membranes and travel through different cellular or tissue compartments before decomposing.[1]

Given that free radicals can cause damage, enzymatic and nonenzymatic antioxidant activities have evolved. Antioxidant enzymes are particularly important for regulating endogenous H_2O_2 (Fig 1)[1] so that it can safely perform its roles, including acting as a secondary messenger in cell migration, proliferation, and apoptosis pathways; transcription factor regulator; chemokine inducer; and pathogen defense mechanism.[2-6] Through these activities, H_2O_2 has a role in the skin, contributing to the innate immune system, apoptosis, wound healing, and superficial vessel tone.[7-9]

There are multiple uses for H_2O_2 applied at supraphysiologic levels from 1% (~300 mM) to 45% (~13.5 M). In this review, we will discuss the applications of H_2O_2 (Table I[10-22]) in addition to important safety considerations. Low concentrations (1%-6%) are used as antimicrobials on intact skin or open wounds. High concentrations (10%-

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45%) are applied to intact skin, delivering a portion of the dose through the stratum corneum (Fig 2).[23] Articles were identified through a PubMed search for the terms *hydrogen* AND *peroxide* AND *skin* AND (*topical* OR *cream* OR *solution* OR *gel* OR *ointment*) in September 2018.

APPLICATIONS

1% to 6% H_2O_2

Skin cleansing/antiseptic. H_2O_2 (3% in the United States, 6% in Europe) has been used since the 1850s for wound irrigation and disinfection and continues to be widely used as an over-the-counter antiseptic against bacteria, yeast, fungi, and viruses.[24,25] To exert its broad-spectrum action, H_2O_2 produces hydroxyl radicals that damage cell components, leading to the breakdown of biofilms, cell membranes, and cell walls.[26-29] Release of oxygen from degradation of H_2O_2, called effervescence, also contributes to its antimicrobial efficacy by loosening debris, pus, and blood in wounds, which reduces bacterial colonization.[30] Compared with antibiotics, H_2O_2 may have a lower risk of bacterial resistance. Ikai et al showed that 7 bacterial species did not develop resistance after 40 exposures to photolyzed 3% H_2O_2.[31] However, exposure to very low H_2O_2 levels can increase resistance. In 1 study, pretreatment of *Salmonella typhimurium* with up to 100 μM H_2O_2 increased resistance on subsequent administration, possibly because of induction of catalase expression.[32] H_2O_2 and generated ROS likely evade resistance by exerting structurally and metabolically widespread oxidant effects.[31]

Outside the United States, over-the-counter creams with 1% H_2O_2 (Microcid, Bioglan Pharma, Malmö, Sweden) or 1% lipid-stabilized H_2O_2 (Crystacide, Mipharm, Milan, Italy) are available to treat superficial infections.[10,11] In a 3-week, randomized, double-blind trial of 256 patients with impetigo contagiosa, 1% H_2O_2 demonstrated reduction in disease severity equivalent to that of the antibiotic Fucidin (LEO Pharma, Ballerup, Copenhagen, Denmark).[10]

Further antimicrobial applications have been explored. One study showed that 3% and 5% H_2O_2 reduced the number of viable cells in *Staphylococcus epidermidis* biofilms on culture plates.[33] Other studies showed antimicrobial synergy of H_2O_2 with iodine[34] and chlorhexidine.[35] Using these antiseptics together may allow decreased dosing with lessened side effects.

Wound care. Endogenous H_2O_2 plays a role in hemostasis,[36,37] initiation of inflammation and neoangiogenesis,[37,38] and cell proliferation.[37,39,40] Given these characteristics, in addition to antimicrobial and debriding properties of H_2O_2, low H_2O_2 concentrations may enhance wound healing.[30,41] However, there are concerns about the cytotoxicity, antiseptic efficacy, and short half-life of H_2O_2.[28]

To explore the antimicrobial efficacy of H_2O_2, Lau and Wong used 3% H_2O_2 on appendectomy wounds before skin closure.[42] Toxic effects were not seen, but H_2O_2 did not reduce infections in treated patients (n = 109) compared with controls (n = 108).[42] In another trial including 48 patients with experimentally induced intradermal blisters inoculated with *Staphylococcus aureus*, application of 3% H_2O_2 did not delay wound healing but also did not decrease bacterial loads compared with the bacterial loads of untreated blisters.[43]

The impact of H_2O_2 on healing rates has also been explored. Two murine studies showed that wound irrigation with 3% H_2O_2 did not delay re-epithelialization[44] or accelerated re-epithelialization compared with saline.[45] As for clinical trials, an early study found that using 3% H_2O_2 every 6 hours on graft donor sites did not delay re-epithelization compared with controls.[45] However, H_2O_2 resulted in air-filled bullae in most patients after healing, possibly from released oxygen lifting the epidermis, suggesting that H_2O_2 should not be applied to newly healed skin.[45] In a later study, bilateral burns were debrided and grafted (N = 49).[46] One limb was washed with 2% H_2O_2-soaked gauze for 5 minutes before grafting, which significantly increased grafting success compared with saline (83% graft take for H_2O_2 vs 66% for saline).[46] Unlike in the earlier trial,[45] H_2O_2 produced no adverse effects.[46] A retrospective study of 130 patients who underwent hydrosurgery involving jet lavage with or without H_2O_2 to debride infected wounds was also done.[47] Patients who were hydrodebrided with H_2O_2 had significantly shorter hospital stays, increased graft viability, and lower postoperative hemoglobin alterations, suggesting that reduced blood loss than patients debrided without H_2O_2.[47]

CAPSULE SUMMARY

- Hydrogen peroxide is an endogenous reactive oxygen species that can be applied topically at supraphysiologic concentrations for therapeutic purposes.
- Hydrogen peroxide is commonly used as an antimicrobial and may promote wound healing, in part via its debriding properties. Recently, 40% hydrogen peroxide was US Food and Drug Administration—approved to treat seborrheic keratoses; other novel uses continue to be researched.

Abbreviations used:

AK: actinic keratosis
H_2O_2: hydrogen peroxide
O_2^-: superoxide
OH^+: hydroxyl free radicals
PDT: photodynamic therapy
ROS: reactive oxygen species
SCC: squamous cell carcinoma
SK: seborrheic keratosis

Treatment of venous insufficiency ulcers with H_2O_2 was also studied. Two 10-day, randomized trials involving a total of 52 patients evaluated daily application of 1% lipid-stabilized H_2O_2. Compared with placebo, H_2O_2 significantly reduced ulcer area, plasma free radicals, and flux on laser Doppler flowmetry, indicating improved microcirculation.[14,15] The improved blood flow may have been due to activation of angiogenesis-promoting metalloproteinases by H_2O_2.[38] A similar study with 73 patients showed that longer H_2O_2 treatment (eight weeks) also reduced venous inefficiency ulcer area compared to vehicle.[16] No adverse effects of H_2O_2 were seen in these trials.[14-16] Therefore, H_2O_2 may enhance wound healing, possibly by improving circulation.

Overall, H_2O_2 does not negatively affect wound healing and may even improve healing. However, use in wound care is currently limited given that H_2O_2 has had mixed results in clinical studies and may not reduce the bacterial burdens of wounds.[42,43]

Acne. Various antiacne H_2O_2 formulations are available outside the United States. Two randomized, investigator-blind trials demonstrated that the efficacies of 1% lipid-stabilized H_2O_2 alone[12] and with adapalene gel[13] are similar to[12] or greater than[13] the efficacies of benzoyl peroxide alone or with adapalene gel, respectively. H_2O_2 also had higher tolerability than benzoyl peroxide.[12,13] Two forms of the H_2O_2-containing product Acnaid (Boderm, Attica, Greece) are available in Europe. The original form, Acnaid Gel Cosmetic, contains 4% H_2O_2, 0.5% salicylic acid, and 4% D-panthenol. A subsequent formulation, Acnaid gel medical device (3% H_2O_2, 1.5% salicylic acid, and 4% D-panthenol), was found to be effective in a small, uncontrolled study and to reduce acne symptoms to a greater degree than the original formulation did.[48,49] The authors proposed that H_2O_2-based formulations may be preferable to topical retinoids that increase sun sensitivity.[48,49]

Skin cancer. H_2O_2 was explored as a photosensitizing agent for photodynamic therapy (PDT), which is commonly used to treat actinic keratoses (AKs) and is effective for some basal cell carcinomas.[50] The production of ROS in PDT leads to tissue damage, so its effectiveness depends on oxygen, which is increased by H_2O_2. Manifold and Anderson studied 1% lipid-stabilized H_2O_2 as a photosensitizer with methylaminolevulinate.[17] Topical methylaminolevulinate (3-hour application) and red light (570-670 nm, 100 J/cm^2) were administered to the forearms of 40 healthy volunteers at low-oxygen, H_2O_2-treated, and control sites.

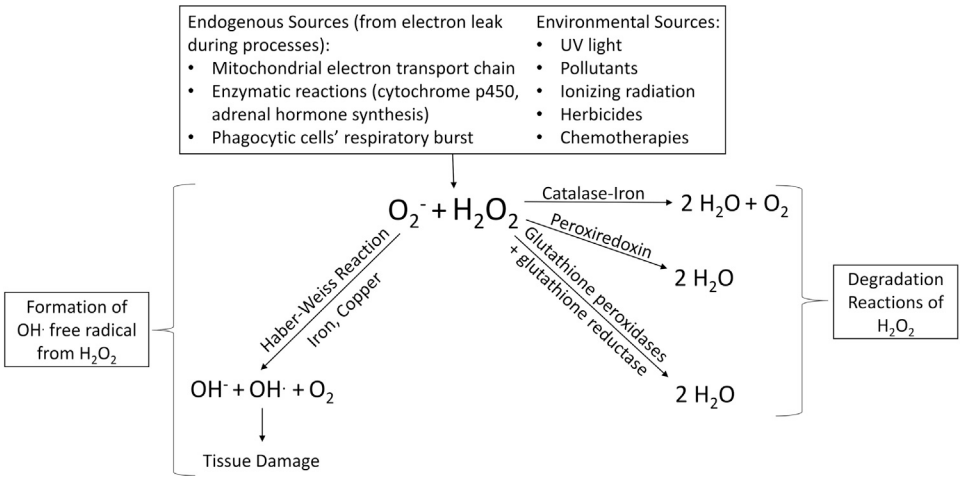

Fig 1. Production and degradation of hydrogen peroxide (H_2O_2). Superoxide (O_2^-) and H_2O_2 are produced from endogenous and environmental sources. Transition metals (iron, copper) can catalyze the formation of hydroxyl free radicals ($OH^\bullet$), hydroxide (OH^-), and oxygen (O_2) through the Haber-Weiss reaction from O_2^- and H_2O_2. $OH^\bullet$ can then react with DNA, proteins, and lipids to cause tissue damage. To protect the body from free radical damage, antioxidant enzymes catalase (complexed to iron), glutathione peroxidases and reductase, and peroxiredoxin degrade H_2O_2 to water (H_2O) and O_2.

Table I. Common applications of H_2O_2

Product	Concentration	Use
Antiseptic/wound healing		
Microcid (Bioglan Pharma, Malmö, Sweden)	1%	Treatment of skin infections (OTC, outside the United States)[10,11]
Crystacide (Mipharm, Milan, Italy)	1% lipid-stabilized	Treatment of skin infections,[10,11] acne vulgaris,[12,13] and venous insufficiency ulcers[14-16] (OTC, outside the United States)
Acnaid (Boderm, Attica, Greece)	4% H_2O_2, 0.5% salicylic acid, and 4% D-panthenol (OTC); 3% H_2O_2, 1.5% salicylic acid, and 4% D-panthenol (prescription)	Treatment of acne vulgaris (OTC/prescription, outside the United States)[48,49]
Various solutions	3% in US; 6% in Europe	Infection prevention for cuts/scrapes/burns (OTC)
Benign and malignant skin tumors		
Crystacide	1% lipid-stabilized	Treatment of skin cancers with PDT (research)[17]
Oxydol (Procter & Gamble, Cincinnati, Ohio)	3%	Radiosensitizer for treatment of unresectable neoplasms (research)[18]
Unnamed gel	25%	Treatment of AKs with sulindac gel (Sigma-Aldrich, St. Louis, Missouri) (research)[19]
Eskata (Aclaris Therapeutics, Wayne, PA)	40%	Treatment of SKs (prescription)[20,21]
Other uses		
A101 (40-45% hydrogen peroxide, Aclaris Therapeutics, Wayne, PA)	40% or 45%	Treatment of common warts (research).
Various solutions	3%-6%	Hair bleaching (OTC)[22]

Availability is noted under use (OTC, prescription, or for research purposes only); products are available in the United States unless otherwise specified.
AK, Actinic keratosis; *OTC*, over the counter; *PDT*, photodynamic therapy; *SK*, seborrheic keratosis.

Oxygen availability was lowered at 1 site by applying blanching pressure with a slide. The ability of H_2O_2 to reverse this deoxygenation was examined by applying H_2O_2 before blanching. Erythema was visually observed and assessed with laser Doppler perfusion imaging, with reduced erythema suggesting decreased PDT efficacy. The percentages of sites showing no visible erythema were 7.5% for the control sites, 7.5% for H_2O_2-treated sties, and 17.5% for the low-oxygen sites. Thus, pretreating with H_2O_2 offset the effects of low oxygen. Laser Doppler perfusion imaging showed that compared with control sites, low-oxygen sites had decreased perfusion after 24 hours whereas H_2O_2 sites had increased perfusion. Thus, H_2O_2 may enhance the efficacy of PDT by increasing oxygen.[17]

H_2O_2 was additionally evaluated as a radiosensitizing agent. Radiation generates oxygen-derived free radicals, so H_2O_2 may enhance radiation's efficacy by increasing ROS. Five patients with superficial, unresectable neoplasms (melanoma, malignant fibrous histiocytoma, extramammary Paget disease, breast cancer, and squamous cell carcinoma [SCC]) were treated with electron beam radiation (48 Gy) 3 times per week for 1 to 3 months.[18] After radiation, the tumors were covered with 3% H_2O_2-soaked gauze for several minutes. Two patients showed complete responses, and 3 showed greater than 50% reductions in tumor volume. No severe complications occurred, but everyone experienced mild radiation dermatitis and/or mucositis.[18] A related study examined intratumor injection of 0.5% hydrogen peroxide and 0.83% sodium hyaluronate as radiosensitizing agents (1-2 times/wk for 3 weeks before radiation) for nonsuperficially exposed neoplasms.[51] Of 11 patients (7 with breast cancer and the others with malignant fibrous histiocytoma, malignant schwannoma, SCC, or fibrosarcoma), 9 patients experienced complete responses, 1 showed a partial response, and 1 experienced no change. These studies support the idea that H_2O_2 may act as a radiosensitizing agent, although larger controlled studies are needed.[18]

25% to 45% H_2O_2

Mechanism. By forming free radicals and oxygen at the stratum corneum, low-concentration H_2O_2 can damage microbial structures and act as a debriding agent. When applied to wounded skin, low-concentration H_2O_2 may penetrate deeper into the skin, exerting further oxidative damage and

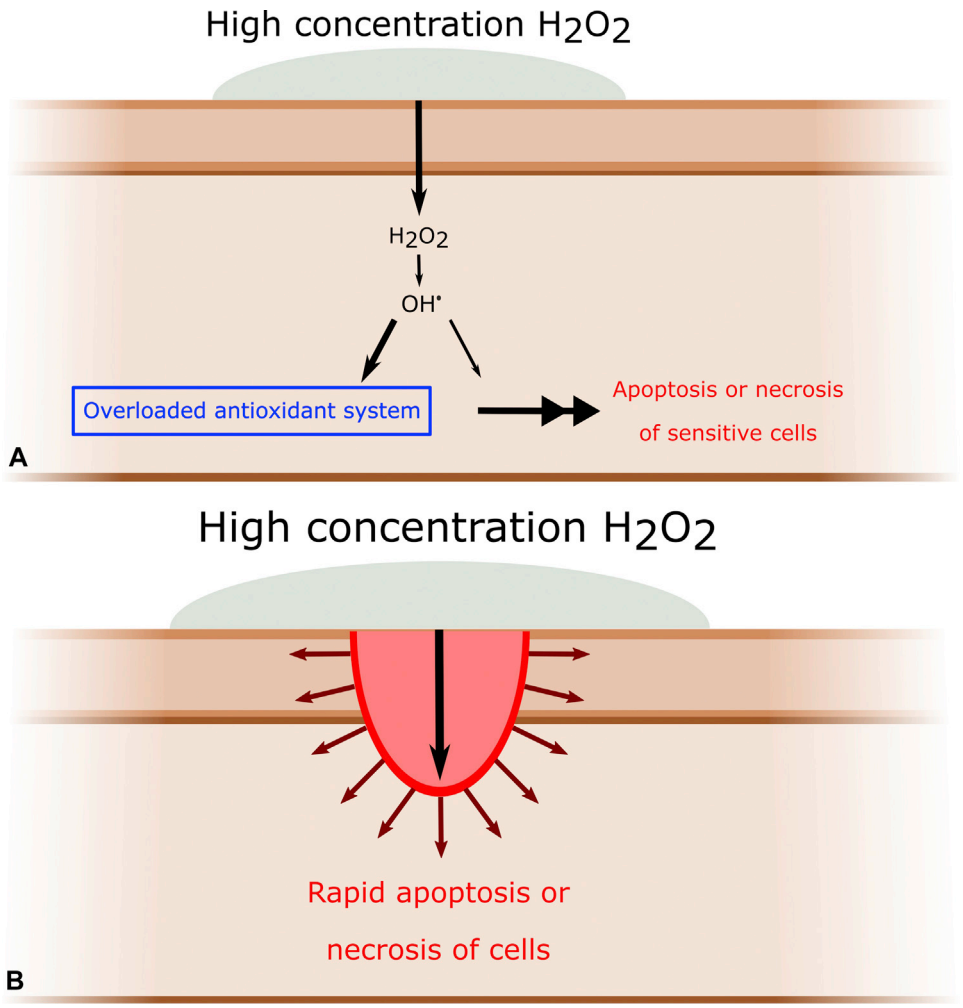

Fig 2. Application of high-concentration hydrogen peroxide (H_2O_2) (10%-45%). **A**, High-concentration H_2O_2 essentially acts as a delivery system—a fraction of the applied dose diffuses through the stratum corneum and into the epidermis, where it breaks down into oxygen and water and is converted to hydroxyl radicals ($OH^{\bullet}$). These free radicals can then overwhelm the skin's antioxidant system and drive oxidative stress–triggered apoptosis or necrosis of sensitive cells. **B**, The stratum corneum acts as a barrier, protecting deeper tissue from high concentrations of H_2O_2 and is thus necessary for safe use.[23] In wounded skin without an intact stratum corneum, high-concentration H_2O_2 will cause rapid necrosis and apoptosis of surrounding cells.

altering blood circulation. In contrast, high-concentration H_2O_2 can be applied only to intact skin[23] and acts as a vehicle, delivering a portion of the dose to the epidermis, where it induces oxidative stress and cellular apoptosis and/or necrosis (Fig 2). High-concentration H_2O_2 is used to treat seborrheic keratoses (SKs) and is being explored for the treatment of AKs. Although the mechanisms by which H_2O_2 eliminates AKs and SKs are not completely understood, consideration of the Warburg effect suggests an explanation. The abnormal keratinocytes of SKs and AKs may be more sensitive to the oxidative stress induced by H_2O_2 than other cells, given that transformed cells experience a shift, termed the *Warburg effect*, from oxidative to glycolytic metabolism even with functional mitochondria. Although the Warburg effect confers certain advantages, it also renders transformed cells more susceptible to even brief exposures of oxidative stress,[52,53] which may explain the superior elimination of abnormal keratinocytes compared with nontransformed cells by H_2O_2.[1,20,54]

SK. Despite SKs being benign, patients frequently seek treatment for them for cosmetic reasons or symptomatic relief.[55] Liquid nitrogen cryotherapy, one of the most common techniques to remove SKs,[56] can cause blistering, scarring, and pigmentary changes, especially in dark-skinned

individuals.[57] Topical treatments, including 40% H_2O_2 (HP40, Eskata, Aclaris Therapeutics, Wayne, PA), which is US Food and Drug Administration–approved to treat raised SKs, may limit these side effects.[20] The efficacy of HP40 for treating 4 SKs per patient was evaluated in 2 phase 3 studies involving a total of 937 patients.[20] Patients received HP40 or vehicle for 1 or 2 treatments depending on their responses. By day 106, significantly more patients using HP40 (4% and 8% per study, respectively) than vehicle (0% in both studies) attained complete clearance of all 4 SKs. A post hoc analysis found that HP40 led to a higher mean per-patient percentage of clear or nearly clear lesions than did vehicle (51% for HP40 vs 7% for vehicle). Additional subanalysis showed that the anatomic location predicted treatment response, possibly because of regional histologic and physiologic differences.[21] The percentage of total SKs graded as clear/nearly clear was higher for the face than for other regions (65% for the face versus 46% for the trunk and 38% for the extremities).[21] Overall, the success of 1 or 2 treatments is limited, producing only about 50% clearance per patient. Further, repeat treatments are almost always needed (97% of the study sample required retreatment), which may be cost-prohibitive for some patients, given that this therapy is not covered by insurance. Adverse effects included only local skin reactions, with most being mild to moderate. Scarring, hypopigmentation, and hyperpigmentation were seen in less than 1%, 3%, and 8% of HP40-treated sites, respectively. However, 98.8% of the patients treated had Fitzpatrick skin types I to IV, so the effects on darker skin could not be assessed.[20] Another study used an *ex vivo* model of human Fitzpatrick type V skin to examine overall cytotoxicity (methyl thiazolyl tetrazolium assay) and melanocyte toxicity (counting of S100-stained melanocytes within high-power fields) of HP40. Compared with cryotherapy (5- or 10-second cycles), HP40 (1 or 2 μL) was less cytotoxic overall and to melanocytes.[58] Therefore, H_2O_2 may be superior for patients with Fitzpatrick type V skin, but clinical trials are needed to compare the efficacy of HP40 and associated risk of pigmentary changes with those of cryotherapy in patients with all skin types.

AK. In a concentration of 25%, H_2O_2 combined with sulindac, an anti-inflammatory agent with anticancer effects, was explored to treat AKs.[19] In vitro studies with SCC cells showed that sulindac and *tert*-butyl hydroperoxide (used for its high stability) together increased cytotoxicity and intracellular ROS compared with either treatment alone. Therefore, consistent with the Warburg effect, the authors theorized that cancer cells will be more sensitive to H_2O_2-induced oxidative stress than nontransformed cells are. In an open-label, uncontrolled study, patients applied sulindac gel plus 25% H_2O_2 daily for 3 weeks. Of 10 AKs, 6 showed partial or complete reductions in size, with 5 of these showing no residual histopathologic involvement. Thus, as in the case of SKs, H_2O_2-derived ROS may reduce AKs.[19]

Common wart. The effectiveness of 40% to 45% H_2O_2 for treatment of common warts is being examined in phase 2 (NCT03278028) and phase 3 (NCT03691831, NCT03687372) clinical trials.

SAFETY

H_2O_2 can be toxic to the skin through oxidative damage and oxygen formation, which can disrupt the epidermis, leading to vacuolar eruptions.[23,59,60] According to a retrospective review of exposures reported to a poison center, low H_2O_2 concentrations caused only transient symptoms, including paresthesias, blanching, and blistering.[61] Although the mechanism of blanching is not fully elucidated, experiments using diffuse reflectance spectroscopy to measure the skin's optical properties have provided insight. Application of 3% to 6% H_2O_2 to the foreams of healthy volunteers did not alter melanin concentrations but caused transient changes in oxyhemoglobin, suggesting that H_2O_2 reached the epidermis and possibly the dermis, where capillaries are located.[62] It is possible, though, that H_2O_2 decomposed in the epidermis and only the resulting oxygen reached the dermis.[62] The authors suggested that H_2O_2 may interact with nitric oxide receptors, causing venule constriction.[63] Consistent with this, an in vitro murine model demonstrated H_2O_2-induced arterial constriction.[64] Rapid breakdown of H_2O_2, however, makes systemic effects unlikely.

Contact with higher H_2O_2 concentrations can cause concentration- and length-dependent adverse effects. Case reports have shown that hair bleaching with 9% H_2O_2 can cause full-thickness scalp burns requiring grafting.[22,65] The mechanism of bleaching-induced damage was explored in human hair and rat skin. Jeong et al applied ammonium persulfate and 6% to 9% H_2O_2 before wrapping hair/rat skin in aluminum foil and heating for 15 to 30 minutes.[66] After 15 minutes, scanning electron microscopy showed that human hair cuticle scales were lifted, removed, or fractured. However, mechanical properties (tensile strength and elongation) did not change. On histology, rat skin showed extracellular matrix damage after 15 minutes and epidermal thinning and subepidermal vesicles after 30 minutes.[66] In another report, prolonged exposure to 35% H_2O_2 through wet clothes resulted in focal epidermal necrosis leading to erythema, purpura,

and bullae.[59] Histologically, collagen and vascular degradation were seen.[59]

Overall, 1% to 6% H_2O_2 causes only transient symptoms, but higher concentrations used for hair bleaching and industrial or experimental applications can cause severe chemical burns.[22,59,65] Caregivers, whether hair stylists, nurses, or physicians, must adhere to product instructions and cease treatments if users experience discomfort.

CONCLUSION

H_2O_2 is used for an array of applications through its oxidant effects and generation of ROS and oxygen. In concentrations of 1% to 6%, H_2O_2 can be used as an antiseptic, to debride wounds, and to promote healing. However, research on the antimicrobial efficacy of H_2O_2 is equivocal; instead, H_2O_2 may be more effective as a debriding agent.[39,46] Similarly, the ability of H_2O_2 to promote wound healing is contentious, with some studies reporting benefit[14-16,46,47] and others not.[42,43] Low H_2O_2 concentrations have also shown value in treating acne, although these products are not available in the United States.[12,13,48] H_2O_2 in concentrations of 25% to 40% are being studied to treat skin tumors. Notably, 40% H_2O_2 is US Food and Drug Administration–approved to treat SKs and may lead to fewer pigmentary changes than cryotherapy does.[20,21,58] Despite these applications, H_2O_2 can cause adverse effects and must be used with caution.

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