Topical stabilized hypochlorous acid: The future gold standard for wound care and scar management in dermatologic and plastic surgery procedures

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Abstract

Background: Hypochlorous acid (HOCl), a naturally occurring molecule produced by the immune system, is highly active against bacterial, viral, and fungal microorganisms. Moreover, HOCl is active against biofilm and increases oxygenation of the wound site to improve healing. Natural HOCl is unstable; through technology, it can be stabilized into an effective topical antiseptic agent.

Aim: This paper focuses on the use of topical stabilized HOCl in wound and scar management for pre-, peri-, and postprocedures—including its ability to reduce the occurrence of hypertrophic scars and keloids. The role of the product in other skin conditions is beyond the scope of this article.

Methods: A panel comprising clinicians with experience in cosmetic and surgical procedures met late 2018 to discuss literature search results and their own current clinical experience regarding topical stabilized HOCl. The panel of key opinion leaders in dermatology and plastic surgery defined key insights and consensus statements on the direction of use for the product.

Results: Topical stabilized HOCl provides an optimal wound healing environment and, when combined with silicone, may be ideal for reducing scarring. Additionally, in contrast to chlorhexidine, HOCl, used as an antiseptic skin preparation, raises no concerns of ocular- or ototoxicity.

Conclusions: For wound care and scar management, topical stabilized HOCl conveys powerful microbicidal and antibiofilm properties, in addition to potency as a topical wound healing agent. It may offer physicians an alternative to other less desirable wound care measures.

KEYWORDS
hypertrophic scars, keloid scars, scar management, stabilized hypochlorous acid, wound care
1 | INTRODUCTION

A topical antimicrobial that decreases the bacterial bioburden of wounds without impairing the ability to heal is a therapeutic imperative.¹ Physicians who perform cutaneous, dermatologic, and aesthetic procedures are focused on rapid healing, minimum pain, and optimal appearance, including minimal scarring.² Therefore, wound care should prevent and treat infection, and minimize inflammation and scarring—all while the antiseptic and healing agent(s) used should be nontoxic to normal tissue.²⁻⁴

2 | HYPOCHLOROUS ACID

Stabilized hypochlorous acid (HOCl), in the form of a physiologically balanced solution (Figure 1),²⁻⁵ exhibits potent antimicrobial activities against a wide range of microorganisms as demonstrated in numerous studies.¹⁻²⁻⁵⁻⁸ HOCl is a naturally occurring molecule produced by neutrophils to destroy pathogens with no evidence of microbe resistance.⁵ This powerful lack of microbe resistance plus proven safety vs normal cells makes topical HOCl a particularly attractive option for surgical wound site antimicrobial activity, especially in cosmetic and medical dermatologic procedures targeting the face.²⁻⁹

3 | ANTISEPTIC AGENTS FOR CUTANEOUS PREPARATION

Common antiseptics used for dermatologic, medical, and/or aesthetic procedures include isopropyl alcohol, povidone-iodine, and chlorhexidine.¹⁰ Isopropyl alcohol, although inexpensive, can cause irritation, is short acting, without enduring antimicrobial activity, and it is flammable. Povidone-iodine is rapidly effective, but neutralized by blood and sputum.¹⁰ As an antiseptic skin preparation, chlorhexidine is used extensively and provides highly effective antimicrobial presurgical skin cleansing.⁶ However, while chlorhexidine has a sustained antimicrobial effect, it has a potential risk of both ocular- and ototoxicity, especially to the middle ear.⁹⁻¹¹ Significant risk of ocular toxicity exists particularly when chlorhexidine is used in periocular areas, which presents a serious challenge to dermatologists, plastic surgeons, and other healthcare providers who treat facial areas.⁹⁻¹¹ If chlorhexidine comes into contact inadvertently with the ocular surface, corneal damage can occur.¹¹

While no direct studies compare chlorhexidine with topical HOCl, no concerns about ocular toxicity with HOCl have been raised. In fact, HOCl was found to be nonirritating and nonsensitizing in various animal safety models.⁵ In a review article on chlorhexidine keratitis, Steinsapir and Woodward⁹ discussed ocular toxicity hazards with chlorhexidine, but did not mention the use of neutral super-oxidized agents such as HOCl.⁷ The panel recognized chlorhexidine’s risk of ocular toxicity as a valid concern to physicians performing facial and cutaneous procedures requiring antiseptics and welcomed the safety profile of HOCl.

4 | ANTISEPTIC AGENTS FOR WOUND HEALING

Data confirm showing HOCl is a potent antimicrobial, a fast-acting anti-pruritic, and a potent anti-inflammatory.²⁻⁶⁻⁸⁻¹²⁻¹³. The panel agreed HOCl’s ability to increase oxygenation (TcPO₂) at the wound site, while breaking down biofilm, is an important key differentiator to other products especially since studies show impaired healing results in chronic wounds or wound dehiscence.⁴⁻⁸

5 | WOUND HEALING—A THREE-PHASE PROCESS

Wound healing is a complex process comprising a well-organized cascade of biological reactions within three interrelated phases—inflammation, proliferation, and remodeling.⁸ These phases involve an intricate progression of cytokines acting upon cellular and extracellular elements in epithelium and underlying mesenchymal tissue.⁴ Yet the phases are not discrete as proliferation begins even before inflammation is completed and continues even as remodeling begins (Figure 2).¹⁴⁻¹⁵

In fact, while the bulk of remodeling is complete within the first year, the strength and appearance of a scar can continue to evolve thereafter.⁶ Due to this ongoing synthesis, wound care and healing must be considered a dynamic process, with minimized scar formation a long-term goal.¹⁴

Evidence suggests skin care immediately before procedure/surgery and throughout the healing phase can have significant effects on healing outcomes; therefore, pre-, peri-, and postoperative management of surgical wounds is crucial to prevent infection, to minimize scar formation, and to reduce the risk for other complications.¹² This is the panel reiterated where HOCl stands out.

6 | BACTERIA, BIOFILM, AND HOCL

Antimicrobial treatment in wound care poses a major challenge because of the creation of biofilm and resistance of microorganisms.¹⁶ Biofilm formation is thought to create a self-perpetuating cycle, prolonging the existence of macrophages and neutrophils in the wound, which in turn impairs normal wound healing and potentially reduces the effectiveness of innate immunological responses.¹⁷⁻¹⁹

However, one significant aspect of the immune system fighting against microorganisms is its ability to generate an effective and rapid response, including formation of highly reactive chemicals, such as hydrogen peroxide (H₂O₂), which is then converted into HOCl during neutrophil activation in the inflammatory phase of wound healing (Figure 3).⁸⁻¹⁰⁻²¹

Numerous clinical studies show HOCl generates various effects to combat microbiotic organisms, including biofilm breakdown.⁸⁻¹⁰⁻²²⁻²⁴ Wang et al.²⁵ indicated HOCl exhibits broad-spectrum antimicrobial activity at concentrations ranging from 0.1 to 2.8 μg/mL and verified
its lethality against a wide range of microorganisms—with the majority of test organisms killed (>99.99%) within the first 2 minutes of exposure.5

Ortega-Pena et al.25 analyzed the effectiveness of different antiseptics to inhibit the various stages of biofilm formation and to disrupt biofilm adhesion in vitro.25 Results reveal chlorine-releasing agents exhibit immediate antibiofilm effects only in the short term but with some resistance,25 while HOCl is shown to be effective in preventing biofilm formation within a short period of time yet demonstrates virtually no toxicity.25
INFLAMMATION, ITCH, AND PAIN IN WOUND HEALING AND SCARS

7.1 | Inflammation

A significant portion of HOCl’s potency is derived from its anti-inflammatory effects, which come from its effect on controlling mast cell response. As part of the immune response to proliferating microbes, mast cells flood the wound site, contributing to inflammation.

A study by Medina-Tamayo et al suggests a neutral pH super-oxidized solution (SOS), such as HOCl, acts like a mast cell membrane stabilizing inhibitor, inhibiting the cell machinery for granule secretion without altering the signal transduction pathways induced by IgE-antigen receptor crosslinking.

Additionally, Sakarya et al demonstrated HOCl solution enhances wound healing in contrast to povidone-iodine, while a study by Dharap et al showed HOCl provides significant improvements in ulcer wound size (and infection), as well as significant reduction in signs of inflammation.

7.2 | Pruritus and pain

Pruritus and accompanying pain are serious and significant concerns with wound healing and for subsequent scar management. Scratching can proliferate the itch/scratch cycle, leading to additional inflammation and an increased risk for scar formation.

In 2013, Pelgrift et al presented an overview of the anti-inflammatory effects of HOCl and proposed two mechanisms by which the product may reduce pruritus: (a) HOCl is microbicidal to cutaneous pathogens, especially Staphylococcus aureus, and (b) is anti-inflammatory, it reduces the activities of histamine, leukotriene B4 (LTB4), and interleukin-2 (IL-2), all of which have been implicated in the pathophysiology of itch.

In fact, in a recent mouse model study of itch and atopic dermatitis, investigators found treatment with HOCl hydrogel prevented the development of eczematous lesions and bouts of scratching. Results indicate a direct reduction in sensory response by HOCl leads to significantly reduced itch and inflammation in vivo. Furthermore, study results indicated 50% of subjects reporting an improvement in pruritus as early as day 1, with 85% of subjects showing significant reductions by day 3 of treatment with HOCl (Figure 4).

7.3 | Wound perfusion

Oxygen plays a critical role in the formation of collagen, the growth of new capillaries, and the control of infection. Perfusion and delivery of O₂ to tissue are closely related.

A study by Bongiovanni investigated effects of topical HOCl in the treatment of patients with venous leg ulcers, including time to wound healing. By assessing micro-circulatory integrity (oxygenation), the author established most patients had elevated transcutaneous oxygen pressure (TcPO₂) levels in peri-wound tissues 15-30 seconds after exposure to HOCl and continued to have elevated TcPO₂ levels some 72 hours after exposure. All venous wounds treated in the study healed, with time to wound closure ranging from 2 to 5 days to ~180 days.

SCAR MANAGEMENT

8.1 | Scar creation

The management of scars is intimately connected to all stages of wound healing, which in turn comprises a multitude of signaling molecules to regulate the complex process of healing on the molecular level. Additionally, continuous collagen production and degradation have an effect of remodeling the mature wound matrix for approximately 6 months postinjury.
Patients with hypertrophic scars (HTS) or keloid formation may have an impaired quality of life specifically from factors including significant itch, pain, and restricted mobility from the scar. Keloids, regardless of the type of injury, share some similarities with HTS, such as development following injury, skin dryness, and itchiness. Recent research suggests both scar types are influenced by chronic inflammation of the reticular dermis.

In the normal maturation phase, when a wound reaches maturity, extracellular cytokines assist in cessation of further collagen fibers, etc. However, a number of genetic and environmental factors can interfere with this "stop" signal, where the lack of negative feedback leads to a continual production of collagen fibers in the wound. Clinically, this response is observed as a HTS. The proliferation of collagen fibers remains self-contained within the original wound margins in HTS.

Conversely, in keloid formation, the scar hypertrophy continues through the later phase of remodeling, between 6 and 18 months, with uninhibited deposition of collagen growing well beyond original wound margins. Therefore, the panel reiterated, early intervention or even prophylactic use of HOCl after incisional procedures may be key to controlling a hyperplastic response.

Because HOCl is known to impact all three phases of wound healing at the cellular level, the combination of HOCl and silicone is being studied for its efficacy in managing and treating HTS and keloids, and for relieving the associated pruritus and pain.

Hypochlorous acid is a safe and effective antiseptic for skin and wound disinfection, while silicone has been used for over 30 years in scar therapy. Even more compelling is that unlike many other
silicone-based products, the combination hydrogel can be applied directly to the wound site in the immediate postoperative period.\textsuperscript{39,40}

Quality of scarring may be improved when post-surgical inflammation and edema is reduced and wound healing is uneventful.\textsuperscript{15} Treatment reducing inflammation post-surgery as early as possible can be expected to result in optimal scarring.\textsuperscript{7,15}

Results from a double-blind, multi-center study were presented to the panel regarding HOCl and silicone in a gel formulation vs a 100% silicone topical agent in patients with HTS or keloids.\textsuperscript{39} The investigators found that pain, itching, vascularity, elasticity, and height of the target scars improved consistently throughout the study for both HOCl and silicone gel and the 100% silicone agent. Trends toward a statistically significant improvement in scar quality compared with baseline were demonstrated for the HOCl and silicone scar management gel (Figure 5).\textsuperscript{39}

Gold et al\textsuperscript{7} also reported on a number of small studies that demonstrated better results with HOCl and modified silicon oil compared to silicone gel regarding appearance of HTS and keloids.\textsuperscript{7} HOCl and silicone gel could be used to treat HTS and keloids early before abnormal scarring begins.

The panel agreed that the spray is to be used during all phases of injection/laser procedures, from preprocedure (removing excess makeup) through peri-procedure (spraying on the face/cold packs) to long-term postprocedure (infection prevention and stimulating optimal healing). When used after resurfacing, the spray is immediately post-procedure applied and combined with an emollient. For at-home care, the spray is used 3-4 times a day for up to 180 days.

The panel members agreed on recommending that R/C is to be reapplied frequently as it dries out more quickly compared with other silicone-based scar gels.

Petroleum jelly or product AQ may be used in combination with R/C to retain more moisture and to prevent the gel from drying out. Additionally, after suture removal a hydrating sunscreen may be used over product R/C.

It is important to show physicians and patients how/why to use the products for optimal results. At night and when in public, R/C should be applied with AQ or petrolatum jelly on top and covered with a dressing (Table 1).

## CONCLUSION

For physicians who perform cosmetic, aesthetic, and medical dermatologic procedures, wound healing and scar management are ongoing challenges; prevention of infection followed by optimal wound care must be followed rigorously to fulfill cosmetically superior needs.
aesthetic outcomes and minimal scars, including HTS and keloids. Panel members acknowledged their own clinical experiences suggest "conventional" options may no longer be ideal. Therefore, the panel concluded, HOCl can be indispensable in pre and peri-procedures as an antiseptic and anti-inflammatory agent, and in postprocedures, including postures, as a wound healing agent. Finally, as a scar management agent preventing or minimizing aberrant scar development well into the remodeling phase, HOCl could become the first line pre and peri-procedure antiseptic for supporting wound healing and scar management.

ACKNOWLEDGMENTS
The literature research for this review was supported with an educational grant of IntraDerm Pharmaceuticals.

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