ORIGINAL ARTICLE

Effect of Stabilized Hypochlorous Acid on Re-epithelialization and Bacterial Bioburden in Acute Wounds: A Randomized Controlled Trial in Healthy Volunteers

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The aim of this randomized controlled trial was to evaluate the wound-healing effect and antimicrobial properties of a novel stabilized hypochlorous acid solution on acute wounds, using a suction blister wound model. One suction blister was raised and de-roofed on each forearm in 20 healthy volunteers. Stabilized hypochlorous acid/control (sterile 0.9% NaCl) solutions were assigned to either wound by randomization. Wounds were irrigated and treated on days 0, 2 and 4. Re-epithelialization was assessed blindly by digital planimetry, and bacterial growth was assessed as the number of colony-forming units cultured from surface swabs. Hypochlorous acid solution increased the degree of re-epithelialization on day 4 by 14% compared with the control solution (95% confidence interval (CI) 6.8–20%, $p = 0.00051$) and was not inferior ($p < 0.0001$) to the control solution on day 10 (0.3%, 95% CI −1.3–1.9%). Median bacterial counts were lower with stabilized hypochlorous acid compared with control and were further reduced after irrigation and treatment of both groups on day 4, but remained lower in the stabilized hypochlorous acid group compared with the control group. This study demonstrates immediate and durable antimicrobial action and a beneficial effect on acute wound healing after irrigation and treatment with a stabilized hypochlorous acid formulation.

Key words: antiseptic; wound management; wound healing; clinical trial.

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SIGNIFICANCE

Antimicrobial compounds are often used in wound management. Although most of these show the desired antimicrobial activities, many are cytotoxic toward cells involved in the wound-healing process. Stabilized hypochlorous acid is a simple, but effective, broad-spectrum antimicrobial compound without known resistance issues when dosed at optimum concentration and duration. In standardized human acute wounds, stabilized hypochlorous acid appears to promote re-epithelialization and control the bacterial bioburden. These findings suggest that hypochlorous acid is a promising antimicrobial agent. Further studies are warranted to identify indications in which uncontrolled bacterial growth is a clinical issue.

Contamination of acute surgical or non-surgical wounds may lead to infection and poor wound healing (1, 2). Irrigation decontaminates wounds, and its effectiveness depends on the pressure and volume of the solution applied (3). Antimicrobial substances are commonly applied in modern wound management.

A novel wound irrigation solution, composed of 0.016% hypochlorous acid (HOCl) stabilized in 0.25% acetic acid (CH_3COOH) buffer at pH 4.2–5.0 (SoftOx Solutions AS, Oslo, Norway) was introduced recently (4). HOCl is indistinguishable from the endogenous substance produced by phagocytic cells. The mode of action of HOCl solution is the physical removal of foreign bodies, debris, and microorganisms through the flushing procedure and by its antimicrobial activity (5). There is a delicate balance between the desired toxicity against microbes without harmful effects on the host cells (6). Cellular studies indicate that stabilized HOCl can increase wound healing at appropriate concentrations (7). In a murine model, stabilized HOCl (0.015%) showed anti-inflammatory effects and beneficial effects on cutaneous wound healing (8). In an exploratory clinical study, irrigation and topical application of HOCl solution to split-thickness skin graft donor sites indicated beneficial effects on epithelialization without raising major safety concerns apart from pain reactions to topical HOCl (4); however, this study was uncontrolled (4).

To follow up on these promising findings, an open-label, evaluator-blinded, non-inferiority, paired study was performed, in which the stabilized HOCl solution was compared with sterile saline (0.9% NaCl; Irriflex, Fresenius Kabi AG, Bad Homburg, Germany). A suction-blister injury wound model was chosen because it allows the assessment of epidermal regeneration without causing scarring (9–16). The primary objective of the current randomized controlled trial (RCT) was to evaluate wound healing, and the secondary objectives

were microbiological control, pain levels and safety with stabilized HOCl vs control treatment. The primary endpoint was the degree of re-epithelialization (%) on day 10. Secondary endpoints included the degree of re-epithelialization (%) on day 4, colony-forming units (CFUs) prior to and after irrigation and treatment on day 4, and the subjective pain level directly after irrigation and treatment on days 0, 2 and 4.

MATERIALS AND METHODS

The study was approved by the Danish Medicines Agency and the Committee of Health Research Ethics in the Capital Region of Denmark (H-20035973) and carried out at the Copenhagen Wound Healing Center, Department of Dermatology, University of Copenhagen, Copenhagen, Denmark, in accordance with the Declaration of Helsinki. The trial was submitted to ClinicalTrials.gov as NCT04771819 on 23 November 2020.

The study design, treatment procedures and assessment of treatment effects are summarized in **Fig. 1**. Inclusion of participants was performed by 2 investigators (EAB and LS). Treatments and clinical assessments were performed by the study nurses.

Participants

The inclusion criteria were subjects in the age range 18–60 years, who had healthy forearm skin, and provided informed written consent. The exclusion criteria were diseases that may interfere with wound healing (e.g. diabetes and autoimmune diseases); active skin disease; daily smoking; pregnancy; systemic immunosuppressive treatment; uncontrolled pain that may interfere with the study outcome as judged by the investigator; allergy to hypochlorous acid, acetic acid or any other remedies/material used; participation in other clinical investigations; inability to read or understand Danish; and any other conditions that may make follow-up or investigation inappropriate or the subject unsuitable for study enrolment. Subjects who met all inclusion criteria and none of the exclusion criteria were included.

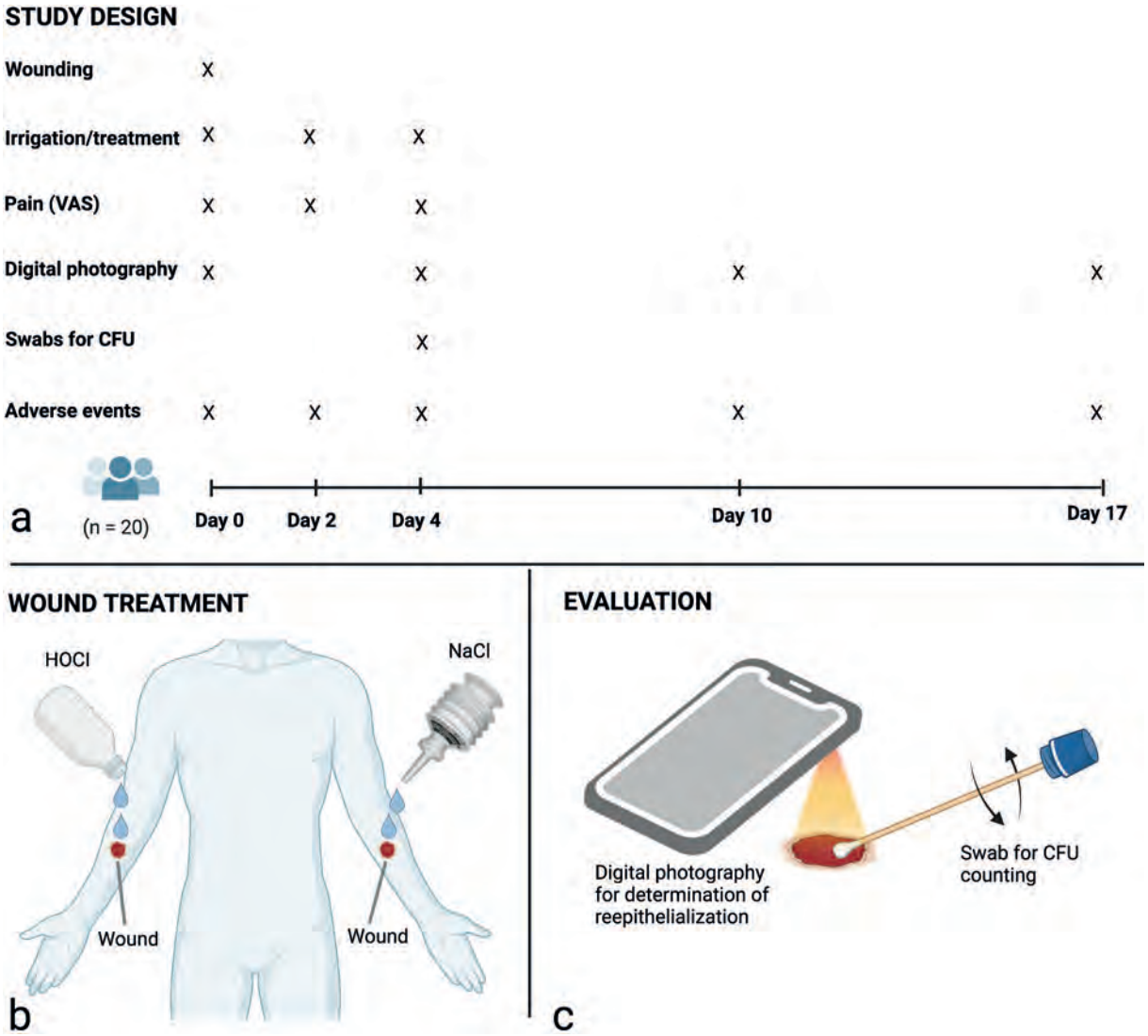

Fig. 1. (a) Study design. (b) Treatments were randomized to the wound on the left or right forearm of the subjects, who served as their own controls. (c) Digital photographs were taken with an iPhone with an attached macro lens (days 0 and 4) or Handyscope (days 10 and 17) for blinded measurements of wound area and determination of re-epithelialization, and a sterile swab was used to quantitate colony-forming units (CFUs). Figure created with BioRender.com (Biorender, Toronto, ON, Canada).

Induction of epidermal wounds

The NP-4 model manufactured by Electronic Diversities (Finksburg, MD, USA) was used to induce 1 10-mm blister in the middle of the volar aspect of each forearm (15, 17). The instrument was set to a negative pressure of 400 mmHg. The epidermal roof of the formed blisters was excised with a sterile scalpel.

Randomization, treatment, and subject-reported pain on days 0, 2 and 4

After induction of the 2 wounds, the wound on the left arm was randomized to irrigation and treatment with either stabilized HOCl or saline control, and the wound on the right arm received the opposite treatment to the wound on the left arm. Randomization codes were obtained from a separate list. The allocation sequence was computer-generated (SAS Statistical Software, SAS Institute, Cary, NC, USA). Distribution of the 2 treatments between the left and right arms was equal in the enrolled subjects. The solutions (i.e. 100 ml stabilized HOCl or 120 ml sterile saline) were poured onto the wound for 5 s from the containers held 10 cm above the wound, as shown in Fig. 1b. Then, the wound was covered for 15 min with sterile non-woven swabs (OneMed, Helsinki, Finland) soaked in the solutions. The subject-reported visual analogue scale (VAS) pain intensity was then assessed on a scale ranging from 0 to 10 cm, where 0 cm was equal to no pain, and 10 cm was the worst imaginable pain for the subject. Finally, the wound was covered with an island dressing composed of a non-adherent absorbent pad in the centre of a vapour-permeable, but water- and bacterial-proof, transparent adhesive film (Leukomed® T plus, BSN Medical GmbH, Hamburg, Germany).

Digital photography and image analysis for determination of re-epithelialization

On days 0, 4, 10, and 17, wounds were photographed before application (day 0) and after removal of the island dressing. Overview images of the wounds and a millimetre scale bar with the subject number, left or right forearm, date, and an arrow pointing toward the hand and parallel to the arm applied adjacent to the wound were acquired by a digital camera (iPhone 5/5S, model: A1753), as shown in Fig. 1c. On days 0 and 4, close-up images of the wounds were taken with a macro lens (21×; Olloclip, Foothill Ranch, CA, USA) attached to an iPhone (18). On days 10 and 17, a Handyscope (FotoFinder Systems GmbH, Bad Birnbach, Germany) was connected to the iPhone (18). The device captures digital images (polarized light) at 20× magnification. A 5-mm calibration scale was included in each image. The wound on the left arm was photographed first.

The digital photographs were imported into ImageJ software (ImageJ 1.52a, NIH, Bethesda, MD, USA) and were analysed twice by a blinded investigator (MSÅ). The wound areas on day 0 ($A_{Day\ 0}$), day 4 ($A_{Day\ 4}$), day 10 ($A_{Day\ 10}$) and day 17 ($A_{Day\ 17}$) were used to calculate the degree of re-epithelialization as a percentage (%) using the following formula (15):

$$\text{re-epithelialization (\%)} = (A_{Day\ 0} - A_{Day\ X})/A_{Day\ 0} \times 100$$

where X=0, 4, 10 and 17.

Bacterial swabs and determination of colony-forming units

Sterile swabs (Σ-Transwab®, MWE, Corsham, UK) were used for sampling from the wounds on day 4 before and after irrigation/treatment with the solutions on both arms, as shown in Fig. 1c. Swabs were rotated at an angle of 45° in the centre of the wound 3 times clockwise and then 3 times anticlockwise (15). The swab stick was then immersed in 1 ml of the Σ-Transwab transportation system medium.

The swabs were processed for CFU determination within 24 h by the Biofilm Test Facility, Department of Immunology and Microbiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. Swabs were vortexed and sonicated for 5 min, and 10-fold dilutions were performed in sterile saline. One hundred microlitres of the samples were applied to 5% horse blood agar plates (Statens Serum Institut, Copenhagen, Denmark) and to blue agar plates selective for Gram-negative bacteria using a modified Conradi-Drigalski diagnostic substrate (4, 15). The plates were incubated for 24 h at 37°C under normoxic conditions. CFUs were counted visually per plate, and the results are expressed as CFUs/swab. The analyses were performed without knowledge of the origin of the swabs.

Sample size calculation

The sample size calculation was based on the primary non-inferiority endpoint that normal wound healing (re-epithelialization in %) after HOCl treatment was not inferior to the control treatment. The Δ (absolute difference in the degree of re-epithelialization) between the HOCl and control was calculated for each subject, where a positive value means more re-epithelialization with HOCl than the control and a negative value indicates the opposite. A Δ value > –10% was considered non-inferior. A standard deviation (SD) of 15% was assumed (10, 14, 15), and with a power of 80% (1–β) and a significance level of 5% (α), 16 subjects were needed. Twenty subjects were included to account for a dropout rate of 20%.

Data management and statistical analyses

Data were entered into an eCRF (Clindox, Sevenoaks, UK) specifically designed for this study.

Continuous variables were analysed using a paired *t*-test. CFU values were not normally distributed and were analysed using the Wilcoxon signed-rank test. The correlation between CFUs before treatment and the degree of re-epithelialization on day 4 was assessed by the Spearman rank-order test. Two-sided statistical analyses were performed using SPSS Statistics 26.0 software (IBM, Armonk, NY, USA). Data are presented as the mean ± SD or Δ with 95% confidence intervals (95% CI) unless otherwise stated. The statistical significance was set to $p < 0.05$.

RESULTS

This RCT compared the effects of stabilized HOCl on wound healing and antimicrobial activity with control in a human wound-healing model.

Participant flow

The recruitment of participants started on 4 November 2020. Twenty remunerated healthy volunteers (age range 18–59 years, 33 ± 12 years), 11 males and 9 females, were included consecutively from 23 November 2020 to 22 March 2021, and the last participant was completed on 8 April 2021. The participants received the allocated treatments except 1 individual who did not attend the day 4 clinical visit due to COVID-19 quarantine, but provided digital images of the 2 wounds. Another participant withdrew from the study after day 10 due to personal reasons and was lost to the day 17 follow-up, but was included in the intention-to-treat population.

Clinical observations

On day 0, confluent blisters had formed in approximately 1.5 h, and the blister roofs were excised. The wound size did not differ ($p = 0.14$) between the HOCl (55 ± 16 mm^2) and control groups (60 ± 15 mm^2).

Stinging, burning or pain reactions were reported by 10 subjects, strongest on day 0 for 9 subjects and strongest on day 4 for 1 subject, immediately after irrigation with stabilized HOCl. These sharp reactions were transient and usually disappeared within seconds. The subjective VAS levels were assessed directly after the 15-min treatment period and were low, with a mean value on day 0 of 0.24 ± 0.52 cm for HOCl and 0.05 ± 0.22 cm for control, values on day 2 of 0.12 ± 0.31 cm for HOCl and 0 cm for control, and values on day 4 of 0.08 ± 0.25 cm for HOCl and 0.03 ± 0.11 cm for control; none of these differences were statistically significant.

All wounds were moist on removal of the protective dressing until day 4. The general impression of the principal investigator (EAB) was that the HOCl-treated wounds were less red than the control wounds. Wound complications were rare, although mild abnormal inflammatory signs were observed on day 2 in 1 wound treated with HOCl and in 2 wounds in the control group. Representative courses of treatment with HOCl and control saline are shown in **Fig. 2**.

Wound-healing measurements

The HOCl solution increased the degree of re-epithelialization compared with that of the control on day 4, with an estimated absolute difference (Δ) in the degree of re-epithelialization of 14% (95% CI 6.8–20%, $p = 0.00051$). The individual re-epithelialization results from day 4 are depicted in **Fig. 3**. On day 10, the estimated Δ was 0.3% (95% CI –1.3–1.9%). The accompanying non-inferiority p-value was < 0.0001 (for primary data see Table SI).

Effect of sex on re-epithelialization day 4

The estimated Δ between males and females was 5.1% (95% CI –10–20%, $p = 0.50$) for HOCl-treated wounds and 1.3% (95% CI –15–18%, $p = 0.87$) for control-treated wounds.

Bacteriology day 4

Surface swabs were taken from day 4 wounds for normoxic culturing before and after treatment. In the HOCl group, bacterial growth was detected in 12 wounds before treatment and in 7 wounds after HOCl treatment. The corresponding figures for the control group were 16 and 15 wounds. Median bacterial counts were significantly lower with HOCl than the control and were reduced after irrigation and treatment in both groups, but remained lower in the HOCl group, as shown in **Table I** (for primary data see Table SII).

Correlation between re-epithelialization and colony-forming units on day 4

There were no significant correlations between CFU and re-epithelialization on day 4 in the HOCl group ($r = -0.073$, $p = 0.77$, $n = 19$) or the control group ($r = 0.21$, $p = 0.39$, $n = 19$).

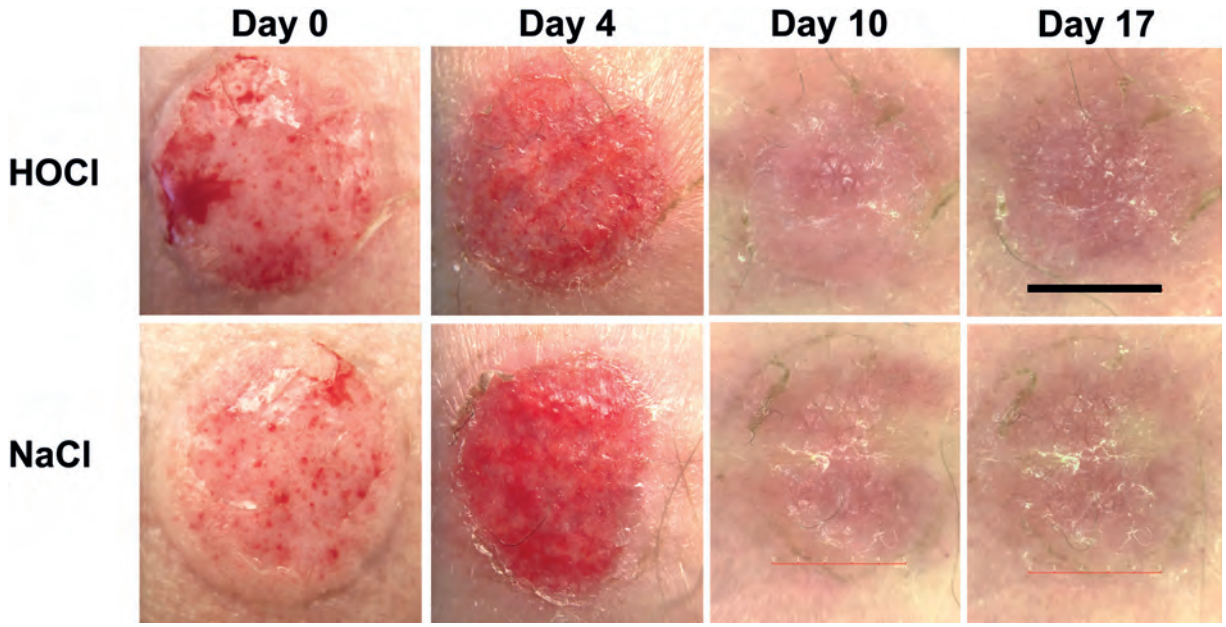

Fig. 2. Course of treatment with stabilized hypochlorous acid (HOCl) or saline control (NaCl) on days 0 (before irrigation and application of HOCl/NaCl), 4, 10, and 17. *Scale bar:* 6 mm.

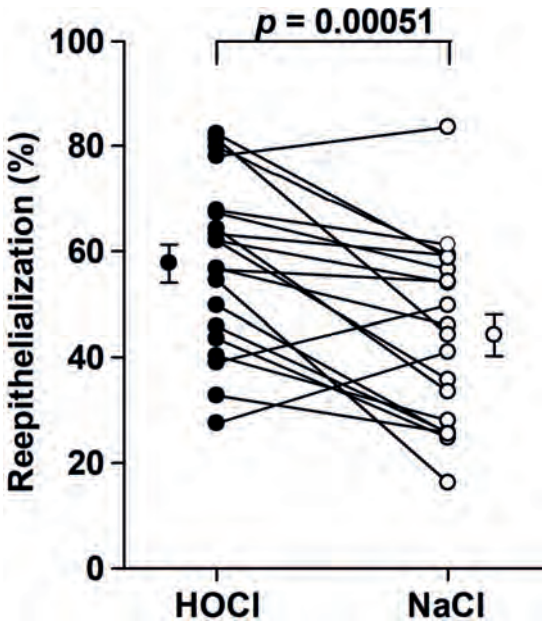

Fig. 3. Re-epithelialization paired data from the 20 volunteers on day 4. Mean ± standard error of mean (stabilized hypochlorous acid (HOCl), 58 ± 3.6%; NaCl, 44 ± 3.8%).

Adverse events

During the study, 8 adverse events were noted and judged unrelated to the HOCl solution; these manifested as mild skin irritation reactions beneath the adhesive film dressing in 4 patients. The other 4 adverse events were erysipelas around the ear in 1 patient, another patient had inguinal skin infection, and the third patient was febrile and had hypertension. No serious adverse events occurred.

DISCUSSION

This RCT demonstrated that wound healing (re-epithelialization) after combined irrigation and treatment with stabilized HOCl was not inferior to that of the saline control on day 10. In contrast, re-epithelialization was accelerated at an earlier stage with the stabilized HOCl formulation. This finding was unforeseen, and it is possible that the early beneficial effect on re-epithelialization resulted in a shortened time to complete wound closure. Daily monitoring between day 4 and day 10 would have been required to detect an effect on the time to complete wound closure.

Table I. Bacterial counts (colony-forming units (CFUs)/swab) on day 4 before and after irrigation and treatment with stabilized hypochlorous acid (HOCl) and the control (sterile saline (0.9% NaCl))

	HOCl ($n = 19$)	NaCl ($n = 19$)	p-value
Before treatment, median (IQR)	70 (0–3,300)	11,500 (20–52,000)	0.015
After treatment, median (IQR)	0 (0–390)	1,100 (10–30,000)	0.0023
p-value	0.023	0.0044	

IQR: interquartile range; CFUs: colony-forming units (derived from 5% blood agar plates. No swarming from Gram-negative species such as *Proteus* sp. was detected; thus, counting the blue plates was unnecessary).

It should be emphasized that the accuracy of the method (digital planimetry) used to determine re-epithelialization has been validated against histological assessment of 60 suction blister wounds on day 4 (15). Evaluation of re-epithelialization on day 4 provides a high degree of sensitivity to detect differences between treatments (maximum sensitivity corresponds to 50% re-epithelialization) (15).

Bacteria have been cultured from this wound type previously and CFUs are higher in wounds than adjacent skin on day 4 (15, 19, 20). The CFUs were significantly reduced in wounds treated with stabilized HOCl than with the control solution, which documents the durable bacterial control with HOCl intervention. In addition, CFU measurements directly after treatment showed a further reduction in the bacterial bioburden. The species recovered from the wounds was not determined. In other studies, the growth of coagulase-negative staphylococci dominated in these wounds (15, 19, 20).

The HOCl formulation contains acetic acid (0.25%) as a pH stabilizing excipient. Acetic acid possesses antimicrobial activity and the minimal inhibitory concentrations of acetic acid against different strains of *Staphylococcus aureus* were determined in the range 0.16–0.31% (21). Thus, the acetic acid component of the HOCl solution may have contributed to the reduced CFUs.

Robson et al. (22) concluded that the increased wound healing with topical HOCl (0.01%) treatment for 30 min of non-infected and infected full-thickness wounds in rats was accompanied by reduced bacterial bioburden compared with that with saline. These beneficial effects were not observed when wounds were exposed to HOCl for 24 h or at higher strengths (22). The current study results for human wounds are strikingly similar to those in rodents. In the same animal model, silver sulfadiazine showed superior antimicrobial activity, but inferior wound-healing capacity, compared with stabilized HOCl (22).

Wound irrigation with saline is an effective method of wound cleansing and prevention of surgical site infections. Reduced bacterial load was documented after saline irrigation, as has been shown in animal wounds (23).

The effect of the microbiota and wound healing per se is debated (24, 25). The current study did not demonstrate a correlation between bacterial colonization and re-epithelialization. Re-epithelialization depends on keratinocyte proliferation and migration (26). *In vitro* tests showed that stabilized HOCl increased the migration of keratinocytes (7). The total activity of collagenase matrix metalloproteinase (MMP)-1 increases more than 100-fold in these wounds (27) and appears to be obligatory for keratinocyte migration (9, 27–29). Interestingly, HOCl can convert non-catalytic latent MMP-1 into catalytic MMP-1 (30) and may thus facilitate the movement of keratinocytes during the re-epithelialization process.

Another possible mode of action of HOCl on wound healing may be attributed to its anti-inflammatory

properties (8, 31, 32), which could advantageously be investigated by sampling cytokines secreted into chambers placed over the wounds and filled with saline (33). Interestingly, HOCl rescued the wound healing ability of keratinocytes derived from the skin of patients with Hailey-Hailey disease by reducing the levels of several pro-inflammatory cytokines (34).

This study has some limitations and strengths. Although the solutions were not masked, the wound areas used for the re-epithelialization calculations were determined by a blinded investigator, and the CFUs were determined in a blinded fashion. Another advantage is that the model allows comparison in the same individual, which eliminates inter-individual differences in, for example, basal cytokine and hormonal levels (35). However, further studies are needed to assess the effect and safety of stabilized HOCl treatment of wounds involving the dermis.

No adverse events related to the use of topical HOCl were observed. The suction blister wound model has been applied to assess pain perception (36). The investigators did not classify the brief immediate and transient sensory reactions after topical HOCl application as adverse events. The high hydrogen ion concentration may have caused these pain reactions via acid-sensing ion channels of nerve endings (37, 38). Hyperalgesia may also be due to the hypotonicity of the HOCl solution. Regardless of causes, the pain scores would probably have been higher if assessed immediately after irrigation of the wounds. HOCl is unlikely to induce antimicrobial resistance.

In conclusion, stabilized HOCl is a promising topical agent for the control of bacterial bioburden and the promotion of wound healing. More studies are needed to elucidate the mechanisms responsible for the observed positive effects of stabilized HOCl on wound healing.

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The authors have no other conflicts of interest to declare.

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Why You Should Add Hypochlorous Acid to Your Skin Care Routine, According to Derms

By Megan Lenzi,Published on February 20, 2024

This powerhouse ingredient is worth the hype.

There are plenty of acids to pick from in the skin care world, but one buzzy one has been standing out from the bunch: hypochlorous acid. From healing wounds to reducing harmful bacteria, this buzz-worthy ingredient fights off acne, rosacea, and much more. Its disinfecting properties are even 100 times stronger than bleach, according to Rachel Lee Lozina, licensed esthetician and founder of Blue Water Spa. We talked to the best board-certified dermatologists and an esthetician to learn all about hypochlorous acid, its benefits, and how to incorporate this ingredient into your skin care routine.

What Is Hypochlorous Acid?

Hypochlorous acid is a multi-use ingredient. "Hypochlorous acid can be found naturally in the body, particularly in the white blood cells, to help fight against foreign bodies and bacteria. It is made up of hydrogen, oxygen, and chloride, offering antimicrobial and anti-inflammatory benefits," explains Dr. Marisa Garshick, MD, FAAD, board-certified dermatologist. The anti-inflammatory and antibacterial benefits address skin conditions such as acne, folliculitis, eczema, and more.

One of the popular reasons people turn to hypochlorous acid in their skin care routine is to treat acne. "It's gaining a lot of buzz in the skincare community for being a superhero in the war against acne," says Lozina.

Hypochlorous Acid Benefits

This buzz-worthy ingredient tackles all sorts of skin care concerns. A major perk: wound healing. This applies to healing many skin conditions and reduces the skin bacteria. "By removing the organisms that contribute to inflammation and skin barrier disruption, it helps heal the skin. It’s safe and gentle making it a great option for wounds and skin conditions like eczema," explains Azadeh Shirazi, MD, board-certified dermatologist.

For those battling breakouts, hypochlorous acid breaks down and slows the growth of harmful bacteria that causes acne. When hypochlorous acid is applied to acne, the bacteria cannot survive, says Lozina. In addition to treating an acne outbreak, it can also kill harmful bacteria surrounding the breakouts, preventing the spread of acne.

How to Use Hypochlorous Acid

Hypochlorous acid is super easy to add into your routine. This skin care ingredient comes mostly in spray form, making it a simple application. "It is best to apply after cleansing, prior to any serums or moisturizers, and can be applied mid-day over makeup or post-workout," explains Dr. Garshick. This product also doubles as a facial cleanser on the go. Booked and busy for a mid-day workout? Spray hypochlorous acid on your skin to clean the skin and prevent harmful bacteria.
This ingredient is especially useful in the cooler, winter months because it can help deal with the stress that cold weather places on the skin. (Think a healthier skin barrier, soothed skin, and reduced irritation.) Hypochlorous acid is gentle on the skin and non-irritating, so this ingredient is generally safe for routine use, notes Dr. Garshick.

Side Effects of Hypochlorous Acid

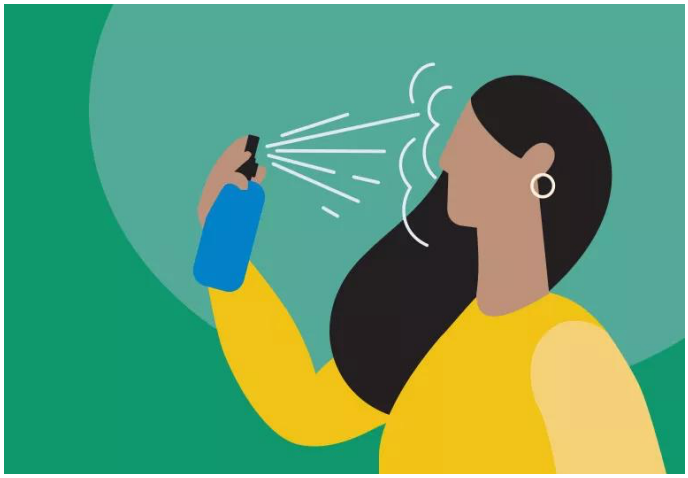
“Just like with any product, some people may react poorly to hypochlorous acid. Dryness, irritation, and itching are reported side effects to the ingredient,” says Lozina. Avoid overusing hypochlorous acid with exfoliating products and other strong skin care ingredients.

Cleveland Clinic

August 2, 2021

What Is Hypochlorous Acid? And Why Should You Use It?

Skin care product can help with acne and fight COVID-19



A tough-sounding acid that's a superhero in the fight against COVID-19 *and* gentle enough to use on your face to treat acne? It might sound like the stuff of comic book legend, but it's real and ready for your medicine cabinet.

The buzz surrounding hypochlorous acid (HOCl) grew by leaps and bounds over the past year given its verified power as a disinfectant against COVID-19.

The hard-core cleaner, however, is also gaining marquee status as an über-sensitive skin care product. For the story behind this miracle product, we turn to dermatologist Shilpi Khetarpal, MD.

What is hypochlorous acid?

Let's start with a basic fact: HOCl exists in your body. It's created by white blood cells as a defense system against infection, bacteria and general ickiness.

HOCl attacks invading pathogens, breaking down the cell walls before destroying unhealthy invaders. The antimicrobial acid is lethally effective in carrying out its protective mission. (Think of it as your own internal Batman.)

"It's your body's natural response to bacteria, and it is very effective at its job," says Dr. Khetarpal.

So how does it end up being mass-produced for cleaning supplies and skin care products? Well, chemists long ago cracked the code to make HOCl by using electrolysis to break down a simple saltwater solution.

More recently, however, manufacturing advancements allowed HOCl to be made in larger quantities with longer shelf life – a key to more widespread use.

How hypochlorous acid benefits your skin
Skin is incredibly tough and durable – a necessity given its role as an outer barrier protecting your inner workings. That front-line role, however, leaves your skin vulnerable to cuts, scrapes and all the bad stuff it's working to keep out.

Dr. Khetarpal says that HOCl offers your besieged skin a little backup by working to:

- Fight bacteria that causes clogged pores and acne.
- Speed up wound healing and repair damage.
- Combat inflammation and conditions such as eczema or psoriasis.

The best part, though? HOCl is nontoxic and handles this hard work while being incredibly mild on your skin. That gentleness is a byproduct of it being naturally produced by your body's immune system. "It's great for sensitive skin," notes Dr. Khetarpal. "It's not going to give you the dryness, burning or irritation of other products [such as alcohol]."

Ways to incorporate hypochlorous acid into your routine
When it comes to at-home use, HOCl typically delivers its benefits by the squirt. Sprays featuring the cleaning agent are widely available. Most are marketed for use on your face, with a focus on treating acne and eczema.

HOCl can be found in other forms, too, including creams and serums.
Products with HOCl can be incorporated into a daily skin maintenance routine to remove bacteria, says Dr. Khetarpal. Sprays also can be used as a quick-hit, on-the-go defense against COVID-19.

HOCl is not a substitute for a basic washing and scrubbing, though. Think of it more like an extra line of defense.

Are there dangers with using hypochlorous acid?
HOCl is billed as being 100x more powerful than bleach when it comes to fighting bacteria. (Yes, it's that potent.) So knowing that, it's really OK to mist the acid over your face without worrying about melting your skin? "There really isn't a risk," says Dr. Khetarpal. "It's safe to use."

Dr. Khetarpal advises that you make sure to verify a product with HOCl is billed for skin care before using it on yourself. If you have sensitive skin, stay away from HOCl products with fragrance. Avoid ingesting HOCl and keep it out of your eyes, says Dr. Khetarpal. Always follow instructions on the product, too.

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REVIEW ARTICLE

JCD Journal of Cosmetic Dermatology WILEY

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 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 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 make 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 peri-ocular 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 Woodward[9] discussed ocular toxicity hazards with chlorhexidine, but did not mention the use of neutral super-oxidized agents such as HOCl.[9] 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 are 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 ($TcPO_2$) 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.[4] 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 (H_2O_2), which is then converted into HOCl during neutrophil activation in the inflammatory phase of wound healing (Figure 3).[8,20,21]

Numerous clinical studies show HOCl generates various effects to combat microbiotic organisms, including biofilm breakdown.[8,22-24] Wang et al[5] indicated HOCl exhibits broad-spectrum antimicrobial activity at concentrations ranging from 0.1 to 2.8 μg/mL and verified

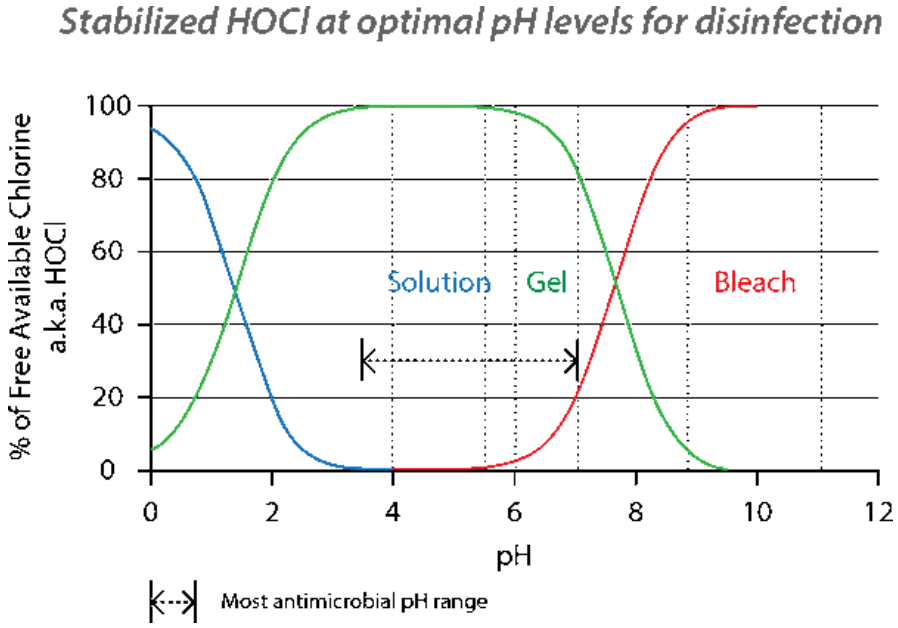

FIGURE 1 Hypochlorous acid at optimal pH levels. Adapted from Wang et al 2007[5]

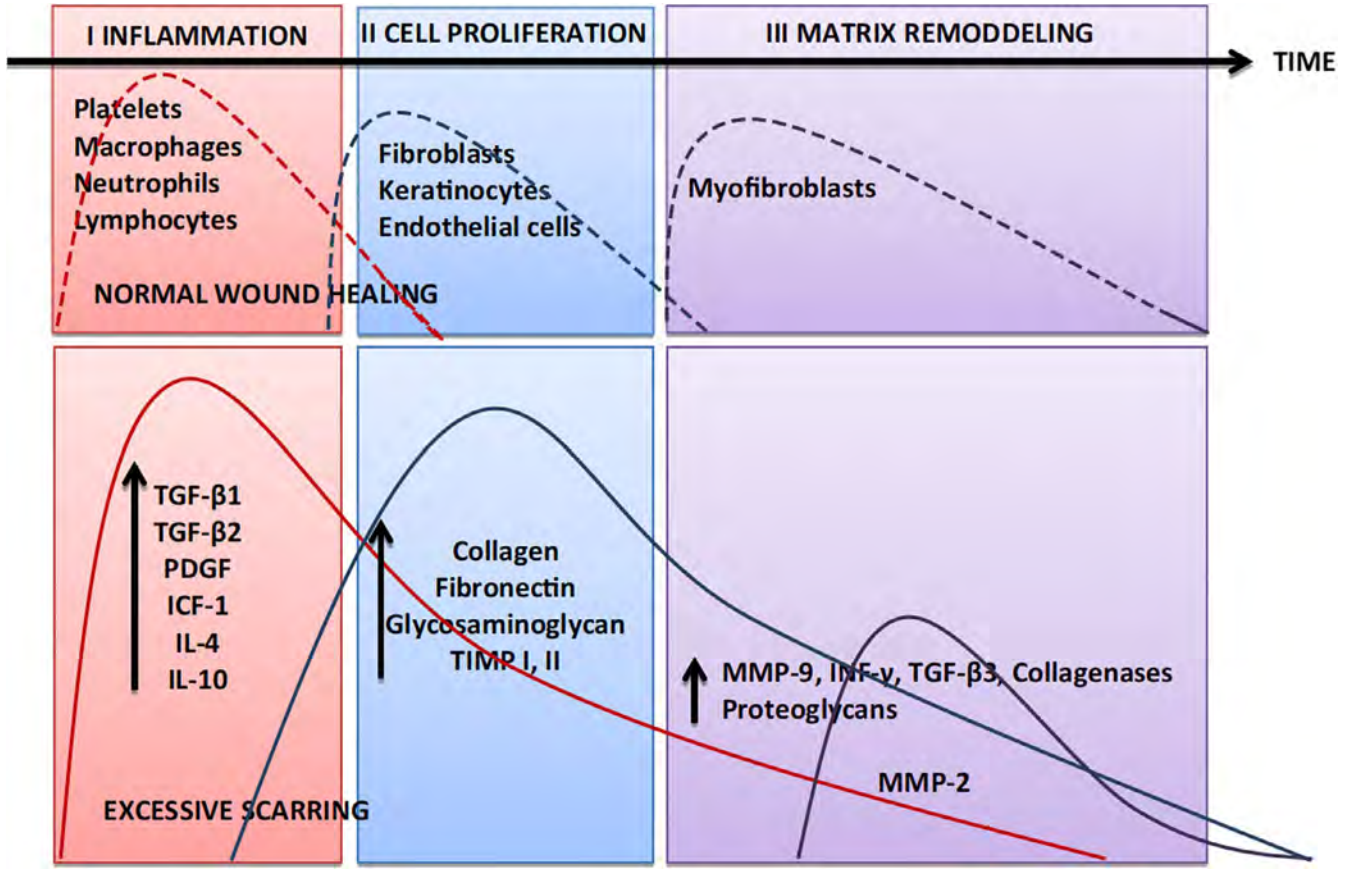

FIGURE 2 Normal wound healing phases vs excessive scarring. Adapted from Gauglitz et al[15]

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]

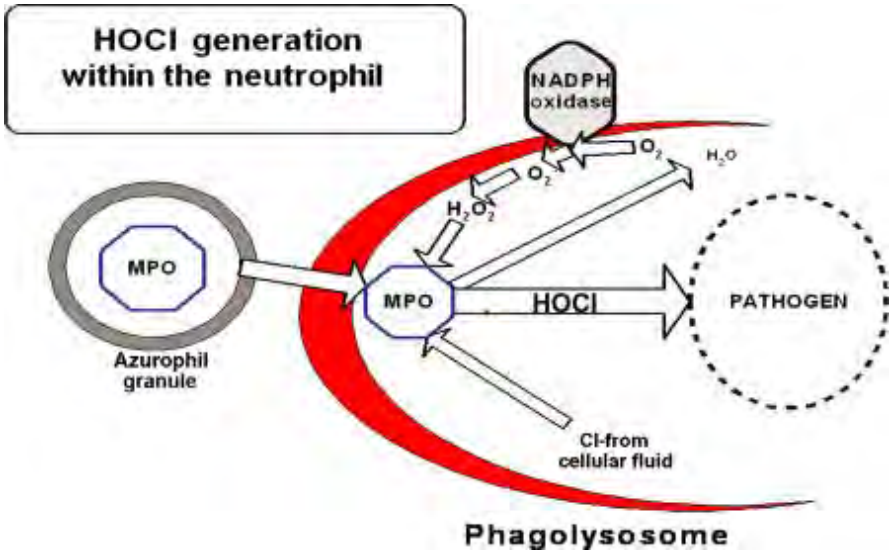

FIGURE 3 Microbicidal generation of HOCl. Adapted from Wang et al 2007[5]

7 | 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[26] 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.[26]

Additionally, Sakarya et al[8] demonstrated HOCl solution enhances wound healing in contrast to povidone-iodine, while a study by Dharap et al[27] showed HOCl provides significant improvements in ulcer wound size (and infection), as well as significant reduction in signs of inflammation.[27]

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.[28]

In 2013, Pelgrift et al[29] 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.[29]

In fact, in a recent mouse model study of itch and atopic dermatitis,[13] 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.[13] 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).[30]

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 O_2 to tissue are closely related.[31]

A study by Bongiovanni[32] 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 ($TcPO_2$) levels in peri-wound tissues 15-30 seconds after exposure to HOCl and continued to have elevated $TcPO_2$ 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.[32]

8 | 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.[14]

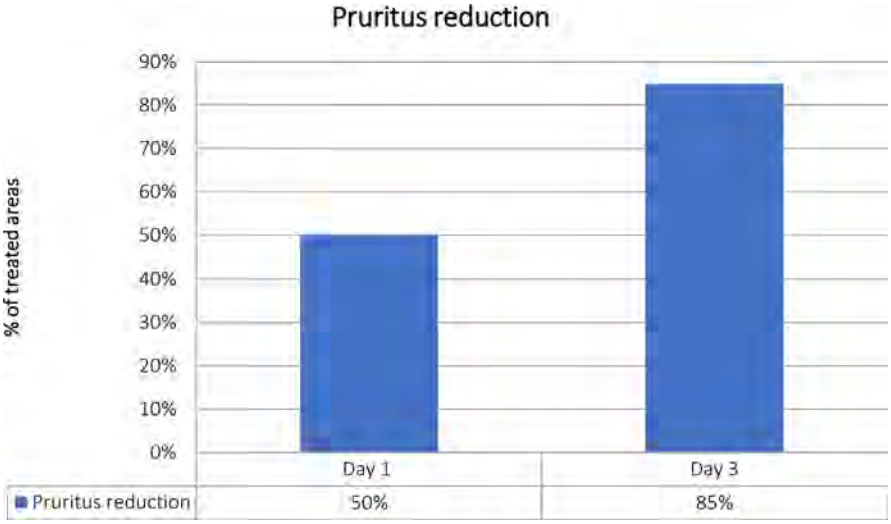

FIGURE 4 Hypochlorous acid reduced pruritus and pain. Adapted from Draelos et al 2012[30]

9 | KELOID FORMATION AND HYPERTROPHIC SCARS

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.[33] Keloids, regardless of the type of injury, share some similarities with HTS, such as development following injury, skin dryness, and itchiness.[4,15] Recent research suggests both scar types are influenced by chronic inflammation of the reticular dermis.[34]

In the normal maturation phase, when a wound reaches maturity, extracellular cytokines assist in cessation of further collagen fibers, etc[14,34] 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 (Figure 2).[14,15] Clinically, this response is observed as a HTS. The proliferation of collagen fibers remains self-contained within the original wound margins in HTS.[4]

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 (Figure 2).[15,35] Therefore, the panel reiterated, early intervention or even prophylactic use of HOCl after incisional procedures may be key to controlling a hyperplastic response.

10 | TOPICAL HOCL AND SILICONE

Because HOCl is known to impact all three phases of wound healing at the cellular level,[8,12,36] 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.[7,37,38]

Hypochlorous acid is a safe and effective antiseptic for skin and wound disinfection,[6,8,29] while silicone has been used for over 30 years in scar therapy.[37] Even more compelling is that unlike many other

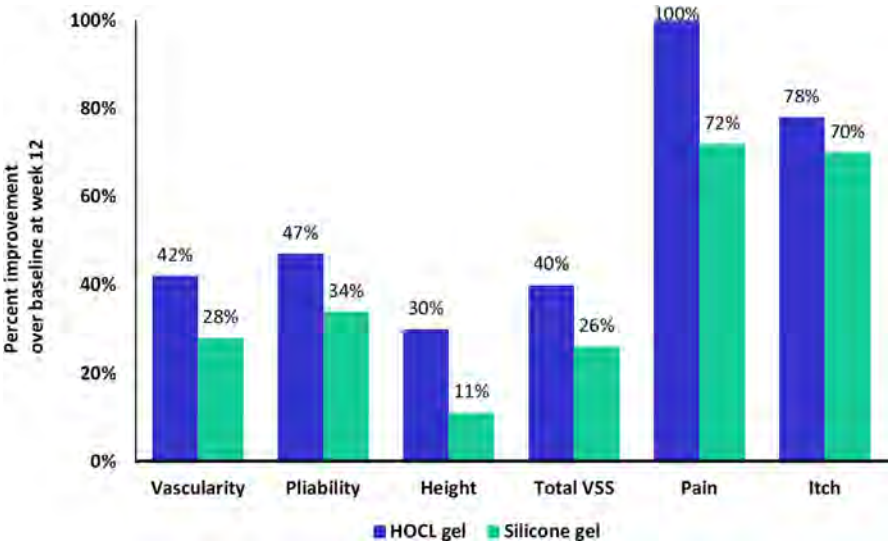

FIGURE 5 Improvement in appearance and symptoms of scars after HOCL use Adapted from Bucko et al[39]

TABLE 1 Consensus regarding the use of HOCl and silicone gel

Type of procedure	Product L	Product R/C	Product AQ
Electro-desiccation and curettage Fractional laser	For preprocedure antisepsis, spray on treatment site and instruments. Intraoperative use of the spray to reduce inflammation. After resurfacing use the spray combined with an emollient. For at-home care 3-4 times a day during week 1.	For at-home care combined with L during week 1 then continue R/C for scar management and to reduce pain.	Combine with R/C for moisturization.
Postshave biopsy and second-intention healing sites	For preprocedure antisepsis use the spray on the treatment site and instruments. Intraoperative use to reduce inflammation.	Cleanse 2-3 times per day with L for 1 wk on the face and 2-3 times per week on the body. For facial shave biopsies, use R/C for 2-3 m. Recommended for a min. of 90 d for sites healing by secondary intention. Use for 180 d for open wounds.	Combine with R/C to provide more moisture.
Postsuture removal	For antisepsis and at-home care.	Recommend R/C for a minimum of 90 d postsuture removal in face-lifts to optimize scar.	

Note: Levicyn™/Lasercyn™ [HOCL spray and gel] (L), Regenacyn™/Celacyn™ [HOCl gel and silicone gel] (R/C), Aquaphor®[41% petrolatum] (AQ).

silicone-based products, the combination hydrogel can be applied directly to the wound site in the immediate postoperative period.[39,40]

Quality of scarring may be improved when postsurgical inflammation and edema is reduced and wound healing is uneventful.[15] Treatment reducing inflammation postprocedure as early as possible can be expected to result in optimal scarring.[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.[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).[39]

Gold et al[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.[7] HOCl and silicone gel could be used to treat HTS and keloids early before abnormal scarring begins.

11 | CONSENSUS REGARDING THE USE OF HOCL AND SILICONE GEL

Panel members discussed their clinical experience using HOCl containing products in clinical practice after which they voted and reached consensus. The following products were discussed: Levicyn™/Lasercyn™ [HOCl spray and gel] (L), Regenacyn™/Celacyn™ [HOCl combined with silicone gel] (R/C), and Aquaphor® [41% petrolatum] (AQ).

Product L is available as a spray and gel and may be used for the reduction of inflammation peri-procedurally and for optimal scar formation management in combination with other products.

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 postprocedure applied and combined with an emollient. For at-home care, the spray is used 3-4 times a day during the first week postprocedure.

The panel members agreed on prescribing product R/C immediately postprocedure and after surgery on sutures for treatment of early scar formation. However, for facelift procedures product use is recommended to start after suture removal and to be continued for a minimum of 90 days. Postshave biopsy, the product is to be used for 30 days, and in case of secondary intent healing wounds, the product is to be used 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).

12 | 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

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 postsutures, 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.

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