ABSTRACT

In-vitro and in-vivo studies have supported antimicrobial, anti-inflammatory, and other biologic properties of hypochlorous acid (HOCl), which has led to its use in the treatment of skin wounds, pruritus, diabetic ulcers, and some inflammatory skin disorders. Research has also shown that the physiochemical properties of HOCl after application to skin are highly dependent on both pH and formulation stability. In this review, the authors discuss a core HOCl formulation (Microcyn® Technology, Sonoma Pharmaceuticals, Petaluma, California) that is stable for up to two years, noncytotoxic, and pH-neutralized to augment therapeutic activity, skin tolerability, and stability. The authors summarize relevant study outcomes and potential modes of action related to this core HOCl formulation, as well as describe its ready-to-use vehicles that are approved and available for topical application.

KEYWORDS: hypochlorous acid, Microdacyn®

Status Report on Topical Hypochlorous Acid: Clinical Relevance of Specific Formulations, Potential Modes of Action, and Study Outcomes

by JAMES Q. DEL ROSSO, DO and NEAL BHATIA, MD

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In this review, the authors discuss a core HOCl formulation (often referred to in the literature as a superoxidized solution or, sometimes, slightly acidic electrolyzed water) that has been termed and marketed as Microcyn® Technology (Sonoma Pharmaceuticals, Petaluma, California; also referred to in some publications as Dermacyn™ from Dyamed Biotech Pte Ltd., Singapore). In this article, we’ve summarized the available studies related to this core formulation, its available vehicles for topical application, its potential modes of action, and in-vitro and in-vivo study outcomes.

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5.5.11 Stabilized/pH-neutral HOCl is superior in stability as optimized over a pH range of 3.5 to 5.5. In highly acidic pH (pH<3.5), the production of multiple byproducts while, in a higher alkaline environment (pH>5.5), much of the HOCl is converted to -OCl.11 In highly acidic pH (pH<3.5), HOCl markedly decreases with the production of multiple byproducts while, in a higher alkaline environment (pH>5.5), much of the HOCl is converted to -OCl.11 HOCl stability is optimized over a pH range of 3.5 to 5.5.11 Stabilized/pH-neutral HOCl is superior in terms of antimicrobial activity to nonstabilized HOCL and acidified bleach in vitro, including against hypochlorite-resistant strains.5,11,21 This cumulative fundamental understanding of the physiochemical properties of HOCl led to the development of the stabilized and pH-neutral core formulation of HOCl solution mentioned previously (Microyn® Technology) and its incorporation into different vehicles that allow for ease of application in clinical practice.8,21 Existing studies evaluating the antimicrobial effects of HOCl are summarized in Table 1. In addition to antimicrobial effects, other biologic properties of HOCl are likely to be clinically relevant. In a variety of laboratory studies, HOCl has been shown to decrease the activity of histamine, neutrophil-generated leukotrienes (i.e., LTβ4), interleukin (IL)-6 and IL-2, and, in high concentrations, to downregulate some matrix metalloproteinases (MMPs) (e.g., MMP-7, collagenases), diminish mast-cell degranulation and cytokine release induced by immunoglobulin E, and induce favorable effects on keratinocyte and fibroblast migration.1,8,11,17,22,23 The reduction of superantigen-producing S. aureus on atopic skin by HOCl application might also be a mechanism for a decrease in cutaneous inflammation associated with both eczematous dermatitis and pruritus in AD.1,9,11 Both antimicrobial and anti-inflammatory/immunomodulatory properties appear to correlate with clinical benefits of HOCl when used for the treatment of various skin disorders, including AD/atopic skin, seborrheic dermatitis, lower extremity diabetic ulcers, pruritus, and acne vulgaris.1,6,11–18 Other clinical applications include promotion of wound healing and scar prevention.14–16,24

**COMPLETED STUDIES SUPPORTING ANTIMICROBIAL ACTIVITY AND OTHER POTENTIAL CLINICAL APPLICATIONS OF HOCL**

There are several publications that include discussion and review of the antimicrobial properties of HOCl and topically applied stabilized/pH-neutral HOCl; methodologies have included preservative time–kill testing, microbial reduction studies on forearm skin with rechallenge, microbial analyses of diabetic foot ulcers, microbial analyses of atopic skin, and skin preparation studies.1–5,9,14–16 Other publications discuss specific clinical applications using a variety of parameters to determine study outcomes. Table 1 depicts details from major studies that address the antimicrobial effects and other therapeutic properties and applications with use of stabilized/pH-neutral HOCl.

**SUMMARY**

HOCl exhibits broad-spectrum antimicrobial activity that is directly toxic to many bacteria and fungi and might also impart antiviral properties. Hypochlorous acid exhibits anti-inflammatory and immunomodulatory properties based on multiple laboratory analyses. These properties appear to correlate with the potential therapeutic benefits of topically applied HOCl for a variety of skin disorders. Topical formulations of stabilized, pH-neutral HOCl (e.g., solution, gel, spray) have been evaluated in several studies demonstrating both antimicrobial effects and therapeutic benefit in many cutaneous disorders, including seborrhoeic dermatitis, atopic dermatitis-associated pruritus, acne vulgaris, diabetic foot ulcers, and hypertrophic scars/keloids. Topical HOCl appears to be well tolerated and safe, without any major adverse events reported.

**REFERENCES**

**TABLE 1. Existing studies evaluating mechanisms of action of HOCl**

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<td><strong>ANTIMICROBIAL EFFECTS</strong></td>
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<td>HOCl vs. water BID for 1 week; HI=20 pediatric subjects; evaluations at 3mins and 7 days</td>
<td>Marked reduction in S. aureus colony counts in HOCl group; no change with water; superior clinical improvement in HOCl group in AD grading (P&lt;0.01)</td>
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<td>In-vivo evaluation of bacterial reductions of S. aureus on healthy foreskin skin (n=8); in-vitro time-kill study vs. different bacterial and fungal isolates; HOCl gel formulation evaluated</td>
<td>Colony counts/log reductions in growth assessed postincubation; rechallenge on 3 or more subjects at later date; total of 60 sites tested in vivo; in-vitro time-kill testing completed on 3 bacterial and fungal isolates at timepoints up to 5mins</td>
<td>99.9% bacterial reduction was shown in in-vitro study inclusive of multiple bacteria (e.g., S. aureus [MRSA], S. pyogenes, Klebsiella spp, P. aeruginosa, Enterobacter spp, Pseudomonas, P. acnes, coagulase-positive staphylococci, others) and Candida albicans</td>
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<td>Bacterial effect markedly greater with HOCl vs. comparators (P&lt;0.05); bacteria reduction did not correlate with available chloride concentration</td>
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<td>Evaluation of stabilized/pH-neutral HOCl solution vs. bacteria resistant to domestic bleach/sodium hypochlorite; comparisons completed vs. unstabilized HOCl solution and domestic bleach</td>
<td>Cell suspensions of fixed colony counts of 10 resistant isolates tested after timed exposures to test products; bacterial reduction compared at multiple timepoints; primary comparison at 2mins</td>
<td>Bacterial reductions with stabilized/pH-neutral HOCl greater and more consistent than comparators; stabilization/pH neutrality shown to increase antimicrobial activity of HOCl; activity of HOCl confirmed vs. resistant bacterial strains</td>
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<td>Bacterial susceptibility, time-kill testing S. aureus, P. aeruginosa, C. albicans; HOCl solution evaluated</td>
<td>MBC testing; time-kil test studying evaluation of complete growth absence; biofilm eradication assessed in growth wells</td>
<td>Rapid time-kil of organisms with MBC range of 1/10-1/1000 biofilm magnitude and organism content within biofilms were decreased; dose-dependent response in a species-specific manner</td>
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<td>Antiviral activity in vitro including enveloped and nonenveloped virus types: assessed poliovirus-1, rhinovirus-1, respiratory syncytial virus, H1N1 and H3N2, West Nile Virus, and Norwalk virus surrogate; HOCl solution evaluated</td>
<td>Target cells infected with HOCl-treated or saline-treated (control) virus exposed for 1min and 5mins; cells in 48-well plate cultures infected with either treated virus, incubated, and evaluated for cytopathic changes at 24–48hrs</td>
<td>Collectively, HOCl-exposed enveloped and nonenveloped viruses decreased by a log, factor ≤5 with exposure of at least 1min; complete virus inactivation occurred within 5mins</td>
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<td><strong>INFLAMMATORY SKIN DISORDERS/PRURITUS</strong></td>
<td>HOCl gel in mild-to-moderate seborrheic dermatitis (n=25) affecting face and/or scalp: open study; monotherapy; gel vehicle with dimethicone 2%</td>
<td>Application BID for 28 days; evaluations included IGA, SGA, pruritus, burning, and stinging</td>
<td>Endpoint success by IGA was 33% at Day 14 and 52% at Day 28; SGA of efficacy/improvement compared with baseline was 62% at Day 28; patients demonstrated improvements in pruritus and decrease in scaling</td>
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<td>HOCl gel evaluated for treatment of pruritus associated with AD (n=29)</td>
<td>Investigator-blinded, randomized 72-hr study; included 19 treated with HOCl BID/PRN and 10 untreated (control); pruritus score of ≥2 on a 4-point scale (AD patients); evaluations included IGA, PGA, and SGA; IGA evaluation included erythema, lichenification, desquamation, and excoriation, and PGA included peeling, stinging, itching, and burning; IGA rich score was linear placement to assess severity (0mm=none, 154mm=most itching)</td>
<td>Mean changes from baseline noted in IGA and PGA were greater in the HOCl arm vs. untreated (control) (P=0.012 and P=0.128); mean % change in IGA rich score was improved significantly in HOCl group (34.76%) compared with untreated (control) group (24.56%) (P=0.007); 73.7% of HOCl group and 30.0% of untreated group noted a reduction in pruritus from baseline to 72hrs.</td>
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<td>HOCl solution evaluated for treatment of facial acne vulgaris (n=87); HOCl solution (n=39) vs. BP (n=24) vs. placebo (n=24)</td>
<td>Double-blind, randomized, placebo-controlled, 12-week study; both actives and placebo applied BID to face; inclusion: 10–50 inflammatory papules/pustules (mean range: 33.5–35.3); no nodules; age range: 15–22 years; 46 women/41 men</td>
<td>Clinical improvements (excellent, good) comparable between HOCl and BP (23% vs. 21% and 54% vs. 90%, respectively); both HOCl and BP were markedly superior to placebo; there was no need for dosage adjustments in any groups and there were no local AEs.</td>
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<td>Open-label study of presurgical response to HOCl solution (n=110) vs. PI solution (n=108) in infected diabetic foot wounds/ulcers; evaluated as part of comprehensive wound care regimen</td>
<td>Alternative assignment to be treated with HOCl or PI + daily dressing changes; baseline and post-surgical colony counts, healing time, and skin reactions noted; baseline number of bacteria similar in both groups</td>
<td>Significantly greater bacterial clearance in HOCl group (P&lt;0.001); significantly shorter median healing time in HOCl group (45 days) vs. PI group (55 days) (P=0.001); no adverse skin reactions in HOCl group (0/110) vs. PI group (18/108)</td>
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<td>Post-surgical therapy of infected diabetic foot ulcers healing by second intention (n=40); HOCl solution evaluated vs. PI + systemic antibiotic therapy and surgical débridement; exclusions included renal failure and immunosuppression</td>
<td>Patients were followed-up weekly over 6mos; evaluation of healing rate, time to negative cultures, duration of antibiotic therapy, number of reinterventions, and AEs were completed</td>
<td>Superior healing rates at 6mos in HOCl group (90% vs. 55%); p&lt;0.01 were noted; significantly shorter time to negative culture and duration of antibiotic use in HOCl group (P&lt;0.05); reinterventions significantly more in number (P=0.05) and reinfestation more frequent (P=0.01) in PI group (9 cases vs. 1 case); no difference was seen in AE rates; both low/safe</td>
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<td>Evaluation of HOCl silicone gel on hypertrophic scars and keloids (n=40); study notpowered for statistical superiority between products (trend analysis possible)</td>
<td>Double-blind, randomized study with TID application of study gel for 8wks (56 days); qualified scars were widespread hypertrophic scars and keloids present for 3–12mos; evaluations at Days 54, 78, 56, 84, and 112 using VAS and symptom scores performed; IGA score and subject satisfaction data at Day 56 (end of therapy) and at Day 112 (end of study) collected</td>
<td>Individual scores for pain and pruritus decreased (improved) in both groups over course of study; mean reduction of scores greater in HOCl silicone group; IGA assessment ratings at Day 55 and 112 very good/good in 6 and 11 subjects in HOCl silicone group and in 5 and 3 subjects in silicone group, respectively; trends showed superiority in HOCl silicone group; no major AEs noted in either group</td>
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HOCl, Hypochlorous acid; AD: atopic dermatitis; BID, twice daily; MRSA: methicillin-resistant Staphylococcus aureus; NBC: minimum bactericidal concentration; HSV: herpes simplex virus; IGA: Investigator Global Assessment; SGA: Subject Global Assessment; PGA: Participant Global Assessment; PRN: when necessary; VAS: Visual Analog Scale; BP, benzoyl peroxide; PI, prednisone iodide; TID, 3 times daily; AE, adverse event; VSS, Vancouver Scar Scale


