With these criteria in mind, this supplement focuses on the Granudacyn (Mölnlycke Health Care, Gothenburg, Sweden) solution and gel products for the cleansing, moisturising and rinsing of acute and chronic wounds.

Granudacyn Wound Irrigation Solution is a pH-neutral hypotonic wound cleansing solution and Granudacyn Wound Gel is an amorphous gel. Both products include the preservatives sodium hypochlorite (NaOCl) and hypochlorous acid (HOCl) in their formulations.

The next article in this supplement reviews the published literature on the use of wound cleansers with HOCl. This is followed by a short section describing the composition and mode of action of Granudacyn Wound Irrigation Solution and Granudacyn Wound Gel. Finally, a number of case studies are presented that describe the use of these products on challenging wounds.

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Wound cleansing: benefits of hypochlorous acid

Joachim Dissemond, MD, Department of Dermatology, Venereology and Allergology, University Hospital Essen, Germany

Cleansing provides an opportunity to remove pathogens from the wound bed, thereby preventing an increase in the bioburden and delayed healing. This article describes the reported efficacy of hypochlorous acid-containing wound cleansers

Hypochlorous acid (HOCl) is a powerful oxidising agent that, depending on the dose and concentration, is capable of damaging multiple cellular components of microorganisms, such as proteins, lipids and nucleotides, simultaneously.[1] It can inflict lethal damage, even in low concentrations, within milliseconds, thereby rapidly and selectively inhibiting the growth and cell division of bacteria and fungi.[2–4]

Introduced in the First World War as a means of treating wound infections, HOCl has a long history of use in wound care. Recently, there has been a resurgence of interest in its use as a wound cleanser.[5] This article describes the biochemistry of HOCl and explores the evidence on its efficacy.

Biochemistry

When chlorine is dissolved in water, a weak acid (HOCl) is produced that, in a further reaction, can dissociate (split into smaller molecules) to form the hypochlorite ion (OCl-). These equilibrium reactions are pH dependent.

$$Cl_2 + H_2O \rightleftharpoons HOCl + H^+ + Cl^-$$
$$HOCl \rightleftharpoons H^+ + OCl^-$$

Cl_2 = chlorine; H^+ = hydrogen ion; H_2O = water;
HOCl = hypochlorous acid; OCl^- = hyperchlorite ion

The microbiocidal activity of a chlorine solution is largely attributed to undissociated HOCl. However, as the pH of the solution increases, the microbiocidal activity decreases, paralleling the conversion of undissociated HOCl to OCl^-. At pH 4–6, HOCl is the predominant species. As the pH increases, OCl^- is formed, and at a physiological pH (around 7.4) HOCl and OCl^- are presented in approximately equimolar quantities.[6]

Mode of action

Antimicrobial properties

HOCl is a naturally occurring bactericidal agent produced by the body's innate immune process. It is released as an endogenous substance by the enzyme myeloperoxidase (MPO) from hydrogen peroxide (H_2O_2) during oxidative burst. (MPOs are expressed by neutrophils; oxidative burst, also known as respiratory burst, releases reactive oxygen species (ROS), whose role is to destroy pathogens.)

The powerful oxidising potential of HOCl results in its reaction with many microbial molecules, especially those involved in growth and cell division, resulting in bacterial and fungal killing.[4] In addition, the modification of microbial cell membrane proteins by HOCl is thought to play a role in HOCl-mediated cell lysis.[7]

Antibiofilm activity

In vitro studies have shown that HOCl has microbiocidal action against bacterial and fungal biofilms, and can disrupt the biofilm extracellular polysaccharide matrix.[2,8,9]

Biofilms are frequently associated with medical procedures involving medical devices and prostheses, diseases such as chronic sinusitis and cystic fibrosis, and infections in hard-to-heal wounds.[10] In fact, biofilms are assumed to be a central factor in the delayed healing of many hard-to-heal wounds.[11] A recent consensus paper stated: 'For wound care and scar management, topical stabilised 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'.[12]

Anti-inflammatory properties

In addition to its microbicidal activity, HOCl has anti-inflammatory and immunomodulatory properties. Laboratory studies have demonstrated that HOCl can:

- Decrease the activity of histamine, neutrophil-generated leukotrienes (LTB4) and interleukins (IL-2 and IL-6)
- Downregulate matrix metalloproteinases (eg, MMP-7 and collagenases)
- Diminish mast-cell degranulation and cytokine release (induced by immunoglobulin E)
- Induce favourable effects on the migration of keratinocytes and fibroblasts.[13]

Protection of human cells from the effects of hypochlorous acid

Importantly, taurine, the most abundant free amino acid in the human body, which is found at especially high concentrations in inflammatory cells such as neutrophils, acts as a scavenger molecule that targets HOCl. In this way, it protects human cells from damage caused by HOCl.[6,14]

Hypochlorous acid formulations for the clinical setting

Technological advances in electrochemical activation processes using salt, such as sodium chloride (NaCl), and water have resulted in the manufacture of stable electrochemically activated solutions (ECAS) containing HOCl that exhibit high tissue tolerability[15] and are not cytotoxic to human cells.[16] These HOCl solutions have several indications within the clinical setting.

Use of hypochlorous acid in wound care

Solutions containing HOCl act as mechanical cleansers for removing debris and microorganisms from a variety of wound types:

- Diabetic foot ulcers (DFUs), leg ulcers, pressure ulcers,[17–22] many of which can be hard to heal
- Acute wounds such as burns, skin grafts,[23,24] soft tissue injuries[25] and surgical wounds[18,24,26,27]

These cleansers can be applied to infected wounds to help reduce the microbial load, thereby reducing the use of systemic antibiotics.[28] They can also be employed as a lavage during surgical procedures to reduce the risk of surgical site infections (SSIs).[18,24,26,27] HOCl solution can also be delivered by instillation with negative pressure wound therapy (NPWT).[29,30,31]

Irrigation solutions containing HOCl can be applied to body cavities, such as the mouth, nose and ears[32,33] and to the eye.[34] Research also indicates that, due to their powerful antimicrobial properties and anti-inflammatory effects,[35] HOCl solutions present a potential tool for wound and scar management,[12] and the treatment of inflammatory skin disorders such as atopic dermatitis.[13,36]

Clinical effectiveness in wound care

A literature search identified 11 published randomised controlled trials (RCTs) that evaluated the use of several ECAS containing HOCl to treat skin grafts, DFUs, surgical wounds and traumatic wounds. A brief overview of each RCT is presented in Table 1.

The different study designs and some low sample sizes limit the generalisability of the results. Nevertheless, it is noticeable that, in all 11 RCTs, use of the HOCl-containing irrigation solutions was associated with positive wound healing results. Several studies reported significantly reduced bacterial bioburden, an improvement in the clinical signs of wound infection and accelerated healing in wounds irrigated with HOCl. Other studies also reported improvements in wound malodour and wound-related pain, as well as a reduction in the length of hospital stay and consequent costs.

Conclusion

The use of HOCl-containing solutions positively influences various aspects of wound healing. They are an easy-to-use and safe method for different types of wounds. However, it should always be noted that, in the long term, treatment can only be successful if the causes of the wound healing

Table 1. Details of randomised controlled trials that have used HOCl-containing wound irrigation solutions

Reference	Wound aetiology	Intervention group(s)	Control group	Outcomes
Foster et al.[23]	Skin grafts	HOCl solution (n=11), (10% TBSA burned)	Mafenide acetate 5% solution (n=8) (6.5% TBSA burned)	Equivalent efficacy (healing at day 14 post-grafting) and safety demonstrated in intervention and control groups. Significantly lower costs in intervention group: cost savings in excess of $406 per patient (after taking into consideration burn size and quantity of solution used)
Sridhar and Nanjappa[17]	Lower limb ulcers (traumatic, DFU, VLU)	HOCl (SOS) (n=34)	PVI (n=34)	Significantly greater reduction in signs of inflammation, microbiological clearance, pain and accelerated healing in intervention group at day 9: ■ Ulcer size reduction: 49% (HOCl) vs 28% (PVI) (p=0.02) ■ Microbial growth reduction: 52% (HOCl) vs 24% (PVI) (p=0.04) ■ Periwound erythema/oedema reduction: 91% (HOCl) vs 70.5% (PVI) (p=0.031) ■ Granulation tissue increase: 100% (HOCl) vs 79.4% (PVI) (p=0.005) ■ Epithelialisation increase: 70.5% (HOCl) vs 41% (PVI) (p=0.015)
Ragab and Kamal[28]	Infected DFUs	HOCl solution (n=30)	H_2O_2 + PVI (n=30)	Significantly greater reduction in infection in intervention group, i.e. infection-free at: ■ Day 10: 70% (HOCl) vs 3.3% (H_2O_2 + PVI) ■ Day 15: 100% (HOCl) vs 13.3% (H_2O_2 + PVI) ■ Day 30: 53.3% (H_2O_2 + PVI) HOCl killed Candida, Proteus and Klebisella species within 15 days, Pseudomonas species after 20 days and MRSA after 25 days. H_2O_2 + PVI failed to kill any of the microorganisms after 30 days
Hiebert and Robson[18]	Infected chronic wounds (PU, VLU, surgical, DFU)	HOCl solution + UD (n=9)	Saline + UD (n=8)	Similar reduction in bacterial bioburden (4 to 6 logarithmic units) immediately following irrigation and debridement in both groups. Significantly greater reduction in bacterial bioburden after day 7 (time of the definitive wound closure procedure) in the intervention group (p<0.05): ■ HOCl + UD: 10^2 log or fewer ■ Saline + UD: 10^5 log Lower rate of postoperative closure failure in intervention group: 25% (HOCl + UD) vs >80% (saline=UD)
Mekkawy and Kamal[37]	Septic trauma wounds	HOCl (0.5% NaCl and 51.5% HCl) (n=30)	PVI (n=30)	Significantly greater reduction in bacterial burden, improvement in wound condition and reduction in pain and malodour in intervention group after 2 weeks: ■ Bacterial load reduction: 90% (HOCl) vs 0% (PVI) (p<0.00001) ■ Proportion of wounds with serous exudate: 100% (HOCl) vs 10% (PVI) (p=0.004) ■ Proportion of wounds with low exudate levels: 100% (HOCl) vs 30% (PVI) (p=0.005) ■ Absence of wound malodour: 100% (HOCl) vs 13% (PVI) (p=0.001) ■ Absence of wound pain: 100% (HOCl) vs 17% (PVI) (p=0.004)

Garg et al.[26]	Peritoneal laparotomy	HOCl (SOS) + saline (n=50)	Saline (n=50)	Significantly more effective lavage of the peritoneal cavity during laparotomy in the intervention group in terms of reducing occurrence of postoperative complications: ■ SSI occurrence: 14% (HOCl + saline) vs 40% (saline) (p=0.0034) ■ Burst abdomen occurrence : 4% (HOCl + saline) vs 16% (saline) (p=0.025)
Landsman et al.[19]	Mildly infected DFUs	HOCl solution (n=21), HOCl solution + AB (n=25)	Saline + AB (n=21)	Higher clinical success rate (cure or improvement), based on clinical signs and symptoms of infection, after 2 weeks with HOCl alone: ■ HOCl: 75% ■ HOCl + AB: 72% ■ Saline + AB: 52% Clinical success rate per pathogen was greatest after treatment with HOCl solution alone after 10 days: ■ HOCl: 80% ■ HOCl + AB: 58% ■ Saline + AB: 64%
Mohd et al.[27]	Stenotomy wounds	HOCl solution (n=88)	PVI (n=90)	Significantly greater reduction in postoperative infection rate (coronary bypass grafting) at 6 weeks in the intervention group (p=0.033): ■ HOCl: 5/88 (6%) ■ PVI: 14/90 (16%)
Piaggesi et al.[20]	Postoperative infected DFU wounds	HOCl solution (n=20)	PVI (50% solution) (n=20)	Significantly greater reduction in bacterial count after 1 month of treatment in the intervention group: 88% (HOCl) vs 11% (PVI) (p<0.05) Significantly greater proportion of wounds healed after 6 months in intervention group: 90% (HOCl) vs 55% (PVI); p=0.002 Significantly shorter healing time (within 6 months) in the intervention group: 10.5 weeks (HOCl) vs 16.5 weeks (PVI)
Hadi et al.[21]	Infected diabetic wounds	HOCl solution (n=50)	Saline (n=50)	Significantly greater proportion of wounds downgraded from category IV (necrotic tissue/pus) to category I (epithelial tissue present) after 1 week in the intervention group: 62% (HOCl) vs 15% (saline) (p<0.05) Significantly greater proportion of patients with a hospital stay ≤1 week in the intervention group: 62% (HOCl) vs 20% (saline) (p<0.05)
Martinez-De Jesus et al.[22]	Infected DFU	HOCl solution (n=21)	Saline with PVI (switch from PVI to surgical soap when infection resolved) (n=16)	Significantly better outcomes in the intervention group reported in this 20-week study: Fetid odour reduction: 100% (HOCl) vs 25% (control) (p=0.001) Cellulitis reduction: 81% (HOCl) vs 44% (control) (p=0.01) Periwound skin improvements: 90% (HOCl) vs 31% (control) (p=0.001)

AB = antibiotic (levofloxacin); DFU = diabetic foot ulcer, H_2O_2 = hydrogen peroxide; HCl = hydrochloric acid; HOCl = hypochlorous acid; MRSA = meticillin-resistant *Staphylococcus aureus*; NaOH = sodium hydroxide; PU = pressure ulcer; PVI = povidone iodine; SOS = superoxidised solution; TBSA = total body surface area; VLU = venous leg ulcer; UD = ultrasonic debridement disorder have been diagnosed and, if possible, treated. A modern moist and phase-adapted treatment that includes HOCl will help support this.

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