

# Comparison of Skin Antiseptic Agents and the Role of 0.01% Hypochlorous Acid

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## Abstract

**Background:** Hypochlorous acid (HA) has both anti-microbial and wound-healing properties with a growing role for utilization in pre-procedural care on the face.

**Objectives:** The authors sought to compare the antiseptic property of 0.01% HA solution, 5% povidone iodine (PI), 4% chlorhexidine gluconate (CHG), and 70% isopropyl alcohol (IPA) antiseptic on facial skin.

**Methods:** This was a prospective single-center clinical trial.

**Results:** A total of 21 participants were recruited. Bacterial growth was seen in CHG (10%), IPA (71%), PI (81%), and HA (95%) of specimens ( $P < 0.001$ ). CHG had less growth compared with HA ( $P = <0.001$ ), IPA ( $P = <0.001$ ), and PI ( $P = <0.001$ ). No difference in bacterial growth was noted between HA and IPA ( $P = 0.063$ ) or HA and PI ( $P = 0.25$ ). Significant differences in mono-microbial and poly-microbial growth were seen between HA and IPA ( $P = 0.046$ ) and HA and CHG ( $P = <0.001$ ). *Staphylococcus epidermidis* grew less frequently in CHG (10%), followed by IPA (29%), PI (71%), and HA (71%). *Staphylococcus capitis* grew less frequently in CHG (0%), followed by PI (14%), HA (24%), and IPA (29%).

**Conclusions:** CHG reduced the bacterial growth compared with HA, PI, and IPA. However, HA, PI, and IPA had insignificant differences in bactericidal effects. Our study provides a supporting role of HA to be considered as an antiseptic.

## Level of Evidence: 2

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Skin antisepsis is an essential measure to prevent surgical site infections, one-half of which are preventable with evidenced-based strategies.<sup>1</sup> Within cutaneous surgery practices, commonly utilized skin cleansing agents vary based on anatomic location and include 70% isopropyl alcohol (IPA), 4% chlorhexidine gluconate (CHG), and 5% to 10% povidone iodine (PI).<sup>2</sup>

Topical cleaning agents applied to the face must be chosen carefully. For more sensitive skin such as in neonates and infants, IPA and CHG may cause irritation or have systemic absorption; therefore, hypochlorite solutions

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are recommended instead.<sup>3</sup> Chlorhexidine is toxic to the cornea and can cause irreversible damage and vision-threatening complications.<sup>4</sup> In the operating room, skin preparation with alcohol-based agents is recommended; however, exposing the cornea to IPA can result in keratitis.<sup>5,6</sup> PI may not be aesthetically pleasing to many cosmetic patients, because the resulting yellow hue can stain the skin and hair if not thoroughly cleaned.

Since the 20th century, hypochlorous acid (HA) solutions have been a well-tolerated antiseptic oxidizing agent.<sup>7</sup> In the past 15 years, HA solutions have demonstrate both antimicrobial and wound-healing properties without cytotoxicity.<sup>8</sup> HA is naturally produced by neutrophils as part of the antimicrobial oxidative burst pathway in response to the invasion of foreign entities. Studies have shown the effect of HA against bacteria, viruses, and fungi, fueling interest in its utilization as an antimicrobial agent.<sup>9</sup> HA has antimicrobial, antipruritic, and anti-inflammatory properties and the ability to break down biofilms. Thus, HA has significant potential for pre- and post-procedural care.

The purpose of this study was to compare the antiseptic properties of 0.01% HA solution (Avenova; Novabay Pharmaceuticals, Inc., Emeryville, CA) with 5% PI (Betadine; Alcon Laboratories, Inc., Fort Worth, TX), 4% CHG (Hibiclens; Mölnlycke Health Care US, Norcross, GA), and 70% IPA (Swan; Vi-Jon, Smyrna, TN) on facial skin.

## METHODS

A prospective, single-center clinical trial was conducted at the University of Miami Bascom Palmer Eye Institute. This study was approved by the University of Miami Institutional Review Board (IRB 20160881) and in accordance with the ethical principles originating from the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Patients were screened in an oculoplastic clinic and enrolled in the study during a 12-month period (December 2018-December 2019). This study was registered on the ClinicalTrials.gov website (NCT02990013). Inclusion criteria included patients over the age of 18 years. Adults unable to consent, minors, prisoners, pregnant women, patients on oral or topical antimicrobial agents, patients with a history of skin infections from injectables and patients without the ability to sit comfortably for 30 minutes were excluded from the study. Written informed consent was obtained.

### Study Design

Utilizing a sterile cotton swab, the skin of the entire right cheek of each patient was tested and placed in thioglycolate broth as a control specimen. The right cheek was subsequently divided into 4 quadrants. Each quadrant was cleansed with either 70% IPA, 5% PI, 4% CHG,

or 0.01% HA for 1 minute and re-swabbed and placed in thioglycolate broth. The tubes were incubated at 36°C to 38°C for a minimum of 72 hours. Each tube was examined for turbidity to assess for the presence or absence of growth. Thioglycolate tubes with growth were vortexed, and 1  $\mu$ L of solution was streaked onto a 5% sheep blood agar plate (Remel; Thermo Fisher Scientific, Waltham, MA) and incubated again at 36°C to 38°C for 72 hours. If polymicrobial colonies were present, the distinct colonies were isolated, re-plated on 5% sheep blood agar, and incubated at 36°C to 38°C for 24 hours. If monomicrobial colonies were present, the colonies were propagated onto a fresh 5% sheep blood agar plate and incubated at 36°C to 38°C for 24 hours.

Within 24 hours of isolation or propagation, the colonies were placed on Trichostatin A slants employing 1- $\mu$ L inoculating loops. The slants were incubated at 36°C to 38°C for a minimum of 72 hours and stored at room temperature. The colonies were then re-plated on 5% sheep blood agar from the slants and incubated at 36°C to 38°C for 24 hours, after which identification and sensitivities were performed utilizing an automated system (VITEK, VITEK 2, BioMerieux, Durham, NC). Utilization of the slants for storage of the colonies allowed the investigators to continue patient recruitment and swab collection and then to perform identification and sensitivities of the colonies in larger batches.

### Statistical Analysis

Statistical analysis was performed by biostatisticians from the University of Miami. The frequency of growth was compared between each of the cleansing agents. For comparison of bacterial growth and specific bacterial species, a Cochran's Q test was utilized to compare differences among treatment agents with a post-hoc analysis employing McNemar's test for pair-wise comparisons. For comparison of mono-microbial or poly-microbial growth, a Friedman's test was employed to compare the differences between the agents, and a post-hoc analysis employing a McNemar-Bowker test was utilized to investigate pair-wise comparisons.

## RESULTS

A total of 21 participants were recruited in the study. [Tables 1](#) and [2](#) illustrate the bacterial growth within the thioglycolate solution and post-hoc analysis. Bacterial growth was noted in only 10% of the CHG specimens compared with 71% of the IPA specimens, 81% of the PI specimens, and 95% of HA specimens ( $P < 0.001$ ). Statistically significant differences in growth were seen when comparing CHG- and IPA-treated skin quadrants to control specimens ( $P < 0.001$  and

**Table 1.** Comparison of Overall Bacterial Growth and Mono-Microbial and Poly-Microbial Growth Between All Treatment Arms

n = 21	Control	HA	IPA	PI	CHG	P
Presence of growth <sup>a</sup>	90% (19/21)	95% (20/21)	71% (14/21)	81% (17/21)	10% (2/21)	<0.001
Mono-microbial growth <sup>b</sup>	10% (2/21)	33% (7/21)	38% (8/21)	48% (10/21)	5% (1/21)	<0.001
Poly-microbial growth <sup>b</sup>	90% (19/21)	62% (13/21)	29% (6/21)	33% (7/21)	5% (1/21)	<0.001

CHG = chlorhexidine gluconate; HA = hypochlorous acid; IPA = isopropyl alcohol; PI = povidone iodine. <sup>a</sup>Cochran's Q test. <sup>b</sup>Friedman's test.

**Table 2.** Pair-Wise Comparison of Overall Bacterial Growth and Mono-Microbial and Poly-Microbial Growth Between All Treatment Arms

	HA	IPA	PI	CHG
Control	1.00	0.031	0.13	$P < 0.001$
HA		0.063	0.25	$P < 0.001$
IPA			0.63	$P < 0.001$
PI				$P < 0.001$
Pair-wise comparison of overall mono-microbial bacterial growth utilizing McNemar's tests to control specimen				
Control	0.031	0.001	$P < 0.001$	$P < 0.001$
HA		0.046	0.12	$P < 0.001$
IPA			0.54	0.002
PI				0.001
Pair-wise comparison of overall poly-microbial bacterial growth utilizing McNemar-Bowker tests to control specimen				

CHG = chlorhexidine gluconate; HA = hypochlorous acid; IPA = isopropyl alcohol; PI = povidone iodine.

$P = 0.031$ , respectively). No difference in bacterial growth was found between HA and IPA ( $P = 0.063$ ) or between HA and PI ( $P = 0.25$ ). Chlorhexidine had significantly less growth than HA ( $P = <0.001$ ), IPA ( $P = <0.001$ ), and PI ( $P = <0.001$ ). No complications were noted from the utilization of each cleansing agent.

Next, the specimens were evaluated for the proportion of mono-microbial and poly-microbial growth (Tables 1 and 2). Poly-microbial growth was seen least commonly with CHG (5%), followed by IPA (29%), PI (33%), and HA (62%). The HA, IPA, PI, and CHG specimens had statistically significantly different proportions of mono-microbial and poly-microbial growth compared with the control specimen ( $P = 0.031$ ,  $P = 0.001$ ,  $P = <0.001$ ,  $P = <0.001$ , respectively). No difference in the proportion of mono-microbial and poly-microbial growth was found between HA and PI ( $P = 0.12$ ); however, a statistically significant difference was noted between HA and IPA ( $P = 0.046$ ) and between HA and CHG ( $P = <0.001$ ). Chlorhexidine had a significant difference in the proportion of mono-microbial and poly-microbial growth compared with all other antiseptic agents ( $P = <0.001$ ).

Frequencies of isolated bacterial colonies present after antiseptic treatment were recorded (Table 3). The most commonly identified bacteria were *Staphylococcus epidermidis* ( $n = 38$ ), *Staphylococcus capitis* ( $n = 14$ ), *Staphylococcus hominis* ( $n = 3$ ), *Staphylococcus lugdunensis* ( $n = 3$ ), and *Corynebacterium spp* ( $n = 2$ ). Analyses were performed on the 2 most commonly isolated bacteria: *S. epidermidis* and *S. capitis*.

*S. epidermidis* grew less frequently on the skin after cleansing with CHG (10%), followed by IPA (29%), PI (71%), and HA (71%). No statistically significant differences were seen in the growth rates for HA vs PI ( $P = 1.00$ ). However, significant differences were found between HA and IPA ( $P = 0.012$ ) and between HA and CHG (0.001). Chlorhexidine had a significant difference compared with HA ( $P = <0.001$ ) and PI ( $P = 0.001$ ) but not compared with IPA ( $P = 0.29$ ).

*S. capitis* grew less frequently on the skin after cleansing with CHG (0%), followed by PI (14%), HA (24%), and IPA (29%). No statistically significant differences were found in the growth rates for HA vs IPA ( $P = 1.00$ ), HA vs PI ( $P = 0.63$ ), or HA vs CHG ( $P = 0.063$ ). No significant differences were seen between PI and IPA ( $P = 0.38$ ) or between PI and CHG

**Table 3.** Isolated Colonies of Bacterial Between Each Antiseptic

	HA, n	IPA, n	PI, n	CHG, n
<i>Staphylococcus epidermidis</i>	15	6	15	2
<i>Staphylococcus aureus</i>	—	—	—	—
<i>Staphylococcus auricularis</i>	—	1	—	—
<i>Staphylococcus caprae</i>	1	—	—	—
<i>Staphylococcus capitis</i>	5	6	3	—
<i>Staphylococcus cohnii ssp urealyticus</i>	—	1	—	—
<i>Staphylococcus hominis</i>	2	—	1	—
<i>Staphylococcus lugdunensis</i>	1	—	2	—
<i>Streptococcus vestibularis</i>	—	—	—	—
<i>Leuconostoc mesenteroides ssp cremoris</i>	1	—	—	—
<i>Staphylococcus warneri</i>	—	1	1	—
<i>Bacillus spp</i>	—	—	—	—
<i>Corynebacterium spp</i>	—	2	—	—
<i>Enterobacter aerogenes</i>	1	—	—	—
<i>Enterococcus faecium</i>	—	—	—	—
<i>Granulicatella elegans</i>	1	—	—	—
<i>Gemella sanguinis</i>	—	—	—	—
<i>Klebsiella pneumoniae ssp pneumonia</i>	—	—	—	—
<i>Pseudomonas aeruginosa</i>	1	—	—	—
<i>Leuconostoc mesenteroides ssp cremoris</i>	—	1	—	—

( $P = 0.25$ ). Chlorhexidine was found to have significant difference in growth compared with IPA ( $P = 0.031$ ).

## DISCUSSION

This in vivo study provides a direct comparison of 4 commonly utilized skin antiseptic agents: 0.01% HA, 5% PI, 70% IPA, and 4% CHG. All 4 agents illustrated their degree of bactericidal effect. The samples from the quadrants treated with CHG were found to have less bacterial growth compared with those treated with HA, IPA, and PI. The difference in bacterial growth, monoclonal colonies, or polyclonal colonies was insignificant between HA, IPA, and PI.

More recently, many formulations of HA have been developed. Because topical application of 1% HOCl cause contact dermatitis, solutions with lower concentrations of HOCl have been designed, including Vashe (0.03% HA; SteadMed, Fort Worth, TX), PhaseOne (0.025% HA solution; IHT, Franklin, TN), OCuSOFT (0.02% HA; OCuSOFT Inc, Richmond, TX), Bruder (0.02% HA; Bruder Healthcare,

Alpharetta, Georgia), Acucyn (0.01% HA solution in dilute saline; Sonoma Pharmaceuticals, Inc), and Avenova (0.01% HA solution; Novabay Pharmaceuticals, Inc., Emeryville, CA). These products vary by packaging material; some are stored in amber light-restrictive glass (Avenova, Bruder) whereas others are stored in plastic, which may diminish the efficacy due to product degradation (Vashe, OCuSOFT). The amber light-restrictive glass allows for a 60-day or 2- to 3-year shelf life with open and closed bottles, respectively.<sup>10</sup> Several studies have shown a dose effect with the bactericidal properties of HA and have found lower concentrations of HA promising in terms of wound healing and antimicrobial properties.<sup>11</sup> Given that no studies, to our knowledge, have been conducted to investigate HA corneal toxicity, we sought in this study to determine the lowest concentration of pure HA approved for the ocular surface housed in a light-restrictive glass container with increased shelf life.

HA 0.01% solution (Avenova; Novabay Pharmaceuticals, Inc., Emeryville, CA) has been FDA approved for cleansing

minor cuts, burns, superficial abrasions, and even large ulcers.<sup>12</sup> This formulation has been well-tolerated along the ocular surface for treatments of dry eye syndrome and blepharitis.<sup>13</sup> When comparing HA with IPA, CHG, and PI, equivalent or superior efficacy was demonstrated through in vitro studies against a wide variety of bacterial isolates.<sup>14</sup> Thus, there is growing potential for HA as an alternative antiseptic for utilization on the face.

Few large, randomized controlled trials have looked at the utilization of HA for skin antiseptics compared with other agents. In a multi-center randomized control trials, CHG was superior to PI in preoperative skin cleansing for general, gynecologic, and urological surgery.<sup>15</sup> Our study had similar results, highlighting the superiority of CHG compared with the other agents. However, on pairwise comparison with HA, PI and IPA did not statistically significantly differ in bacterial growth. Other studies have compared topical HA formulations with other antiseptics in various contexts. In patients treated for large infected diabetic foot ulcers, those treated with HA experienced a shorter healing time compared with those treated with PI.<sup>16</sup> In studies investigating *Ralstonia picketti* biofilms on silicone breast implants and irrigation samples from surgical breast augmentation, HA showed increased antimicrobial activity.<sup>17,18</sup>

Unlike the bacterial biome in other parts of the body, the bacterial diversity along the conjunctiva and eyelids is not well-characterized. Recolonization within 20 minutes along the eyelid margin can occur following an application of HA; thus, some studies have advocated for twice-daily applications.<sup>12,19</sup> The most commonly isolated bacteria along the eyelids in blepharitis patients include *Corynebacterium*, *Staphylococcal* isolates (particularly *S. epidermidis*), and *Propionibacterium acnes*.<sup>20</sup>

In our study, the most frequently isolated species after antiseptic application were *S. epidermidis* and *S. capitis*. The bacterial growth after application with HA and PI did not significantly differ; however, CHG-treated samples were found to have significantly less growth than the others. Two other studies utilized 0.01% HA for in vitro studies against bacterial isolates and biofilms on contact lenses.<sup>13,21</sup> The bactericidal activity was over 99.9% at 10 minutes for *S. capitis* and at 30 minutes for *S. epidermidis* on biofilm specimens after application of HA.<sup>18</sup> Looking at in vitro studies specifically studying bacterial isolates, *S. capitis* and Methicillin-susceptible *S. epidermidis* were killed immediately after application of HA and IPA; however, 1 minute of inoculation was required for CHG and PI before the full bactericidal effect.<sup>13</sup>

Examination of the literature reveals a promising future role for HA. The utilization of Vashe (0.03% HA) in colonized wound beds allowed for skin graft salvage with decreased bacterial concentrations.<sup>22</sup> In 1000 cases of soft-tissue

filler injections, the authors of one study reported no cases of soft-tissue filler infection after employing 0.01% HA solution as a cleansing agent for 30 seconds prior to injection.<sup>23</sup> Topical formulations of HA have an emerging role pre- and post-procedure to optimize patient outcomes.<sup>24</sup>

Several limitations exist within this study. Our initial testing conditions may not translate directly into clinical care until larger, randomized, prospective studies are conducted. This study offers a small sample size that may not represent the diverse skin biome of an entire population. The study did not take into account the patients with facial hair or chronic make-up utilization that may affect skin biome. This study was limited to testing only 0.01% HA and did not investigate higher doses such as 0.025% PhaseOne, 0.03% Vashe, and 0.02% ocular cleansers such as Bruder and OCuSOFT that may have the potential for higher efficacy given the dose-dependent bactericidal activity that has been shown. However, there are currently no studies that have evaluated corneal toxicity with HA; thus, it is unknown if these higher concentrations may lead to corneal keratitis. Further studies are needed to evaluate which formulation of HA may be superior. The contact time of each cleansing agent was 1 minute; however, in standard surgical operating room practice, the solution is left to dry for a standard 3 minutes. The plating of the tests was performed at 72 hours after inoculation and was not conducted in a blinded fashion, which may allow for potential bias. This possibility was minimized by assuring calibrated loops and standardized testing were performed in a consistent manner at each step. Additionally, the identification and antibiotic sensitivity testing was performed only once for each isolated colony. Given the wide range of speciation with bacterial growth for each patient, the statistics comparing the agents were mostly descriptive on categorical variables of bacterial growth. The isolated species corresponding to each cleansing product varied between patients; however, this may be related to the strong bactericidal effects these cleansing agents possess.

## CONCLUSIONS

The application of CHG significantly reduced the bacterial growth compared with HA, PI, and IPA. However, all 4 cleansing agents showed antiseptic property compared with our controls. Our study provides a supporting role for HA to be considered as an antiseptic with products currently available. Further studies looking at the corneal toxicity of the 0.01% HA concentration and large randomized controlled studies comparing the infection rate after facial injectables with each available antiseptic agent are needed.



## Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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