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Major article

Chlorhexidine is a better antiseptic than povidone iodine and sodium hypochlorite because of its substantive effect

Juan H. Macias MD [a,*], Virginia Arreguin MD [a], Juan M. Munoz MD [a], Jose A. Alvarez MD [a,b], Juan L. Mosqueda MD [a], Alejandro E. Macias MD [a,c]

[a] University of Guanajuato, Leon Guanajuato, Mexico City, Mexico
[b] Research Department, Hospital Regional de Alta Especialidad del Bajio, Leon Guanajuato, Mexico
[c] National Institute of Medical Sciences and Nutrition "Salvador Zubiran," Mexico City, Mexico

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Background: The present study compared both the antiseptic efficacy of sodium hypochlorite against that of chlorhexidine gluconate in isopropyl alcohol and the substantive effect of chlorhexidine, povidone iodine, and sodium hypochlorite.

Methods: This was a 2-step study that included volunteers. In step 1, 4 skin areas were tested for bacteria in colony-forming units (CFU): 2 were controls to determine baseline bacteria or the effect of scrubbing, and 2 were treated with 10% hypochlorite or 2% chlorhexidine in isopropyl alcohol. Every subject was tested 4 times. The second step tested the substantive effect of 10% povidone-iodine and the aforementioned antiseptics.

Results: For the first step, 30 volunteers were studied, resulting in 120 determinations for each control and antiseptic. No differences between chlorhexidine gluconate (median 115 CFU/cm^2) and sodium hypochlorite (median 115 CFU/cm^2) were found. Both antiseptics were significantly different from rubbing control (317 CFU/cm^2) and basal control (606 CFU/cm^2). Only chlorhexidine showed a substantive effect.

Conclusion: We consider that chlorhexidine gluconate in isopropyl alcohol, sodium hypochlorite, and povidone-iodine is equally effective for procedures that do not require a long action. However, chlorhexidine is desirable for procedures such as catheter insertion, skin preparation for surgery, or handwashing prior to surgery.

Antiseptics are one of the most powerful weapons in infection control. Their clinical impact has been proved since the nineteenth century, when Ignaz Semmelweis introduced hand hygiene with a sodium hypochlorite solution, leading to an impressive reduction in morbidity and mortality related to childbed fever.[1] In Mexico, every year, 450,000 new cases of hospital-acquired infections are reported, with 32 deaths per 100,000 habitants and associated costs of 1.5 billion US dollars.[2] Nearly one-third of these infections could be prevented with asepsis and antisepsis protocols as well as hand hygiene.[3-5]

Nowadays, available antiseptics are limited because many of them have been removed from the clinical practice because of their toxic effects or infection outbreaks from intrinsic and extrinsic contamination.[6,7] Antiseptics more commonly used for health care are alcohol, chlorhexidine, and iodine compounds. Alcohol has resisted the test of time, having only rarely been associated with contamination; it has an extended spectrum of activity and rapid action, although it is volatile and flammable, requiring sealed containers to keep the ideal concentration. Povidone-iodine has considerable spectrum and has been used for decades, with only few problems of contamination with gram-negative bacilli and allergic reactions[8,9]; it is still the standard of use in many institutions through the world. In a previous study, we reported that the antiseptics properties of sodium hypochlorite are not inferior to those of povidone-iodine.[9]

Chlorhexidine is currently recommended for skin preparation before surgery and insertion of intravascular devices[5,10,11]; nevertheless, chlorhexidine is an expensive substance, which limits its availability and distribution, especially in developing countries.[9] Chlorhexidine has an inherent substantive effect, which is the ability of only a few antiseptics to remain linked in its active form to

* Address correspondence to Juan H. Macias, MD, Universidad de Guanajuato, 20 de Enero 929, Leon Guanajuato, Mexico.
E-mail address: aaeemmhh@yahoo.com (J.H. Macias).
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certain biologic surfaces such as the stratum corneum of the skin.[12] Thus, the surface acts like a reservoir of the antiseptic leading to a prolongation of its bactericidal effect.[1,13-16] Substantivity is an important characteristic that could explain the reported superiority of chlorhexidine against other antiseptics. Nevertheless, substantivity has been poorly studied because almost every study design tested indirect methods such as bacterial counts within specific periods after the antiseptics application.[13,14,16,17-21] Because bacterial counts may represent only a delay in population recovery, a new method that could overcome this concern is needed.[22]

The present study was conducted to compare the antiseptic efficacy of 10% sodium hypochlorite against that of 2% chlorhexidine gluconate in 70% isopropyl alcohol in healthy volunteers. Additionally, we conducted tests to prove an eventual substantive effect of chlorhexidine, povidone iodine, and sodium hypochlorite. With the results of the present and those of a previous study,[9] we expected to gather information to conclude whether chlorhexidine has an immediate antiseptic effect and substantivity similar to that of sodium hypochlorite and povidone-iodine.

MATERIAL AND METHODS

Experimental design

The study was designed in 2 steps to answer 2 main research questions. The first step compared the antiseptic efficacy of sodium hypochlorite and chlorhexidine. The second step tested the substantive effect of sodium hypochlorite, chlorhexidine, and povidone-iodine.

The first step was a phase 3 nonrandomized efficacy study in 2 arms of human volunteers, blinded to the outcome assessor. Healthy adult volunteers with no history of skin allergies or atopy were included between April and December 2011. The main outcome measure was the bacterial counts in cultures of skin treated with chlorhexidine or with sodium hypochlorite. The secondary outcomes were the presence of allergy or skin reaction. The second step evaluated the substantive effect of chlorhexidine, sodium hypochlorite, and povidone-iodine. The protocol was reviewed and approved by the investigation board of the University of Guanajuato, Department of Medicine and Nutrition, and registered in clinicaltrials.gov (NCT01321125). Signed informed consent was obtained from each participant. The sponsor had no involvement in the design or conductions of the investigation.

Study products

Two products were used to test the main outcome: a standard agent, 2% wt/vol chlorhexidine gluconate in 70% vol/vol isopropyl alcohol (ChloraPrep, Enturia, TX), and 10% wt/vol sodium hypochlorite of electrolytic production (Except; Pisa SA de CV, Guadalajara, Mexico). To test the substantive effect, the same products were used, in addition to povidone-iodine 10% wt/vol (Isodine; Boehringer-Ingelheim Promeco SA de CV, Mexico City, Mexico).

First step

Preparatory phase

For stabilization of the skin microbiota, all volunteers used neutral soap and shampoo without antiseptics over a period of 2 weeks, being advised to avoid swimming in pools. After that phase, every subject was assessed to check that he or she had at least 100 aerobic bacteria per square centimeter of the forearm skin, which was be determined before entering the study. Volunteers were instructed to not take a shower 24 hours prior to the experiment.[23]

Methods of intervention

For the primary measurement, 4 areas of approximately 25 cm^2 each were selected from the forearms. Two areas were designated as controls; the first one, the basal control, was used to determine the baseline bacterial count; the second one was the rubbing control; a cotton swab impregnated with sterile saline solution was rubbed to test the influence of the rubbing itself into bacterial counts. The other 2 areas were rubbed with chlorhexidine or sodium hypochlorite. Rubbing control or antiseptics were rubbed with circular movements toward the periphery, covering the area of study; solutions were left on the skin for 60 seconds before culturing, allowing them to dry. To conclude the trial, every volunteer had to be examined 4 times, each one separated by at least 15 days, alternating the areas in every subsequent test; therefore, every area was used for both controls, and for each antiseptic. All the volunteers were instructed to keep using the neutral soap and hair shampoo without antiseptics during the entire follow-up period.

Microbiologic methods and neutralizer

Cultures were performed by the same trained technologist, following the quantitative technique described by Williamson and Kligman.[24] Briefly, a scrub cup of 5 cm^2 of internal area was pressed over the skin zone to be tested. With the use of a pipette, the technologist added 3 mL of broth (Neutralizing broth D/E; DIFCO, Mexico City, Mexico) containing a neutralizing agent for halogens (0.1% sodium thiosulphate) and chlorhexidine (L-α-lecithin) and a detergent agent (1% solution Tween-80) as washing solution. A sterile rubber policeman (a hand-held flexible natural-rubber scraper attached to a glass rod) was used to rub the skin for 2 minutes. After this, 3 mL of new washing solution was added, and the abrasive scrub was repeated. These 2 washes were gathered together, and 50 μL of this volume was dropped on a plate containing neutralizing agar (Neutralizing agar D/E; DIFCO), which has the same characteristics of the neutralizing broth. The solution was distributed across the surface using a sterile plastic spreader. The plates were incubated at 35°C ± 2°C for 24 ± 4 hours in ambient atmosphere. After incubation, the outcome assessor counted the colonies to determine the colony-forming units (CFU) per square centimeter (CFU/cm^2) of skin.

Second step

Method for testing the substantive effect

To test the substantive effect, 3 fingers were selected and then washed; the first finger was swabbed with chlorhexidine, the second one with povidone-iodine, and the third one with sodium hypochlorite. The antiseptics were left to dry for 60 seconds, followed by a second wash with distillate water, to remove any antiseptic excess. Finally, each finger was covered with a sterile dressing. After 2 hours, the dressing was removed, and the fingertips were tested, placing them delicately for 30 seconds on a Mueller-Hinton agar (BD/BBL; Mexico City, Mexico). The plates were swabbed with a 0.5 McFarland solution of *Escherichia coli* ATCC 25922. Finally, the plates were incubated at 35°C ± 2°C for 24 ± 4 hours in ambient atmosphere. After incubation, the outcome assessor searched for inhibition zones.

Statistical analysis

To test significant differences in non-normal distribution data, we used a range test (Kruskal-Wallis) with 3 degrees of freedom, corrected for ties. A post hoc test of Kruskal-Wallis for multiple comparisons of z values was used to determine which arm was different. The α level for significance was established at 5%. For the first step, a minimal sample of 16 volunteers was calculated to find a difference of 100 CFU/cm^2, with a power of 80, and bilateral error