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Effectiveness of the Topical Use of Chlorine Dioxide in Patients with Skin Infection at the Reina Catalina Clinic, Barranquilla, Colombia

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Abstract

Introduction: Skin and Soft Tissue Infections (SPI) occur very frequently in hospital services and complicated cases require hospitalization or immediate interventions in hospitalized patients. However, there are few studies in our setting that describe new treatments for these infections.

Material and methods: Prospective descriptive observational study of patients with episodes diagnosed with post-traumatic, diabetic, mixed (diabetic/traumatic) ulcers delayed wound healing and burns in postoperative patients in the plastic surgery unit of the Reina Catalina Clinic in Barranquilla, Colombia from July 2022 to November 2022.

Results: Fifteen (15) cases of hospitalized patients with picture of post-traumatic, diabetic, mixed (diabetic/traumatic) ulcers, delayed wound healing and burns with the presence of skin and soft tissue infections (IPPB). The most frequently diagnosed entity was cellulitis/erysipelas (60%); the origin of the IPPB was hospital and the majority of patients did not present comorbidities. None of the patients evaluated presented any vascular disease that could alter the results. The most frequently isolated microorganism was *P. aeruginosa* (40%), *P. mirabilis* (20%), *E. coli* (20%) and *E. cloacae* (20%), all of nosocomial origin. During the treatment, no patient died and all of them completely healed from their IPPB.

Conclusion: The most frequently treated IPPB in patients hospitalized at the Reina Catalina clinic in Barranquilla are mainly ulcers associated with cellulitis/erysipelas, most of them acquired by nosocomial route. The use of new and old antibiotics have not had the expected success, especially due to the presence of biofilms that favor the aggravation of infections. Chlorine dioxide solubilized in water at 3000 ppm topical, had a result of complete resolution of nosocomial infections in the area of plastic surgery, which makes it a promising substance in the resolution of infections in postoperative, traumatic and ulcer wounds. diabetes and burns in particular in the treatment of the biggest problem associated with these infections: The biofilm.

Keywords: MeSH • DeCS • Chlorine dioxide • Biofilm • Disinfection • Soft tissue infections • IPPB • Wounds and injuries • Translational medicine

Introduction

The present investigation was carried out in order to verify the effectiveness of the topical use of chlorine dioxide as a bactericidal agent in patients with skin infections at the level of ulcers, wounds and burns of intrahospital origin that occurred at the Reina Catalina Clinic in the city of Barranquilla, Colombia and managed by the plastic surgery service of said institution, through the application of chlorine dioxide solubilized in water at 3000 ppm mixed with sterile saline solution. The management of skin infections, particularly post-surgical ones, are especially challenging because these infections are often emergencies with complications that put the patient's life at risk and require immediate surgical and therapeutic intervention. In any case, tissue trauma, whether caused by surgical or non-surgical wounds or burns, as well as chronic ulcers, compromises the host's local defenses and provides an ideal environment for the invasion and multiplication of bacteria. Even with modern asepsis and sterilization of surgical environments, material and human equipment, the risk of bacterial and fungal contamination of postoperative wounds remains high, whether due to traumatic wounds, surgery, or ulcers. Surgical Site Infections (SSIs) occur after surgery, in an area of the body where surgery was performed. SSI is the most frequent complication of surgery and an important source of clinical and economic problems for health systems since many microorganisms show resistance to common and uncommon antimicrobials [1].

The most important bacteria implicated in skin infections are *S. aureus* and *S. pyogenes*. Other bacteria that cause skin infections less frequently are *S. agalactiae* (GBS) (<3 months), Large Negative Bacilli (NGB), Clostridium and other anaerobes (as in necrotizing fasciitis), as well as other opportunistic bacteria, including atypical mycobacteria. In recent years, there has been an increase in the incidence of skin and soft tissue infections caused by Methicillin-Resistant *S. aureus* (MRSA) by 70% worldwide [2,3] (Table 1).

The usual treatment of wound infections in plastic surgery is immediate intervention in the operating room to perform tissue lavages and debride, especially for patients with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene. Empirical antibiotic treatment should be comprehensive (vancomycin or linezolid plus piperacillin-tazobactam, or plus a carbapenem, or plus ceftriaxone and

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Table 1. Classification system for skin and soft tissue infections [3].

Class	Description
1	Simple infection without systemic signs or symptoms indicating dissemination* and without uncontrolled comorbidities that may complicate treatment; amenable to outpatient management with topical or oral antimicrobials.
2	Infection with systemic signs or symptoms indicating dissemination* or with stable comorbidities, or infection without systemic dissemination but with uncontrolled comorbidities; may require hospital management or parenteral antibiotics.
3	Infection with signs or symptoms of systemic dissemination* or uncontrolled comorbidities; Hospital management with parenteral antibiotics is required.
4	Life-threatening** infection with signs of systemic sepsis requiring parenteral antibiotics; hospital management is required (possibly in intensive care unit), surgery may be indicated.

metronidazole). Penicillin plus clindamycin is recommended for the treatment of documented necrotizing fasciitis due to group A *Streptococci*. Topical treatment with mafenide acetate, silver sulfadiazine, bacitracin/neomycin/polymyxin, 2% mupirocin, along with systemic anti-pseudomonal antibiotics and anti-staphylococcus should be reserved for documented or clinical infections [4].

In wounds, especially chronic ones, a biofilm forms. A biofilm is defined as: "An organized microbial ecosystem, made up of one or several species of microorganisms associated with a living or inert surface, with complex functional and structural characteristics". This type of microbial formation occurs when cells adhere to a surface or substrate, forming a community, which is characterized by the excretion of a protective adhesive extracellular matrix. It has been observed that these communities are present in chronic wounds (up to 80% of them may have biofilms) and their organization and structure mean that we have to approach their identification and approach from a different perspective.

All open wounds are considered to be contaminated. Consequently, as devitalized tissue appears in the lesion, this wound bed favors bacterial proliferation. As the bacterial load (bioburden) increases, the demands on the host's immune system also increase. In response, if the bacterial load in the wound is not suppressed by the host's defenses, then the load will continue to increase. The increase in the amount of bacteria in the wound will increase the risk of clinical and systemic infection which will occur unless appropriate measures are used such as debridement of devitalized tissue in surgery usually under sedation or general anesthesia and administration of topical antimicrobials/ systemic (Figure 1).

Biofilms are complex microbial populations that secrete an extracellular polymeric substance that adheres them to the wound bed and protects them from the host's immune system and from antiseptics and antibiotics. This polymeric matrix is made up of proteins, polysaccharides and extracellular DNA. Biofilm is made up of bacteria, which represent 15%-20% of the volume and a matrix or glycocalyx, which would represent 75%-80%. This matrix is composed of a mixture of exopolysaccharides, proteins, mineral salts and cellular material [5-9]. They constitute a chronic inflammatory state that prevents healing. Subsequently, the biofilm reaches a larger size, which causes certain areas of the biofilm to detach, spread and colonize other locations in search of nutrients, because its growth limits the nutrients in the wound bed, thus forming new biofilms. This biofilm that sows the surface of the wound bed forms in hours, reaching maturity in a period between approximately 48 and 72 hours, as it varies depending on the type of fungus or bacteria in question (Figure 2).

The biofilm prevents the normal growth, granulation and epithelization of the tissue, in addition to acting as a physical barrier in the healing process and involves 80% of bacterial infections in humans. The following is the process of formation of a biofilm:

1. Reversible adhesion to the surface, the initial phase, carried out by a solitary microorganism (planktonic state).
2. A correct action in this phase by the healing team will prevent the creation of biofilm.
3. Irreversible adhesion to the surface: the phase in which microorganisms begin to multiply and organize themselves to ensure the survival of the formed community, Biofilm / protective matrix and its dissemination to other areas.

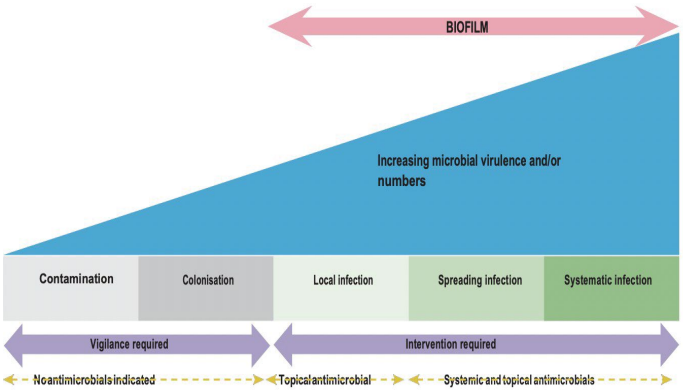

Figure 1. Infection development process (Continuum).

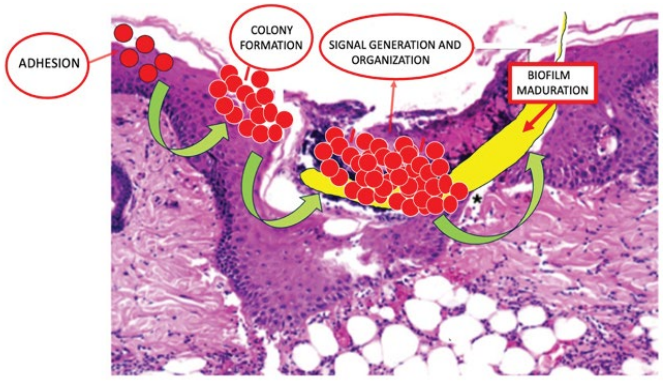

Figure 2. Process of biofilm generation.

Experimental evidence suggests that the biofilm formation process is regulated by a complex cascade of regulators. An investigation carried out with *P. aeruginosa* demonstrated that the biofilm formation process is regulated by a quorum sensing or autoinduction process. The quorum sensing system is a regulation mechanism dependent on the accumulation in the environment of a signal molecule, autoinducer, which allows the bacteria to sense the population density of existing bacteria. In gram negative bacteria the main autoinducer is acyl homoserine lactone, while in gram positive bacteria the autoinducer is peptides. When a sufficient amount of the autoinducer accumulates in the extracellular medium.

In addition to regulation at the transcriptional level, there are numerous indications of the existence of a post-transcriptional regulation of the biofilm formation process. Thus, the activation of cellulose synthesis in *S. typhimurium* is produced by the allosteric activator c-diGMP. The concentration of this activator depends on two enzymatic activities, diguanylate cyclase and phosphodiesterase, associated with enzymes that contain the GGDEF and EAL18 domains. In *S. typhimurium* there are at least 21 proteins that contain these domains and it is unknown if all these proteins affect the regulation of the cellulose synthesis process under different environmental conditions or if they are responsible for other functions. Within the enzymes of the process, hydrolases play an important role. The Ntn-hydrolase superfamily is composed of very diverse enzymes with different substrate specificity, but all of them have the common characteristics that they are capable of hydrolyzing amide bonds,

which have a nucleophilic catalytic residue in the N-terminal end and that acquire their active form after undergoing an autocatalytic cut.

All members of this protein superfamily share the same amide bond hydrolysis mechanism. Initially, the nucleophilic oxygen or sulfur of the N-terminal residue (Thr, Ser, or Cys) donates its proton to the α-amino group and then nucleophilic attack occurs on the carbonyl carbon of the substrate, giving rise to a residue-stabilized tetrahedral intermediate. From the oxyanion hole of the enzyme. Subsequently, the α-amino group of the nucleophile donates its proton to the nitrogen of the cleaved peptide bond, giving rise to a covalent bond with part of the substrate and releasing the amino product. In the second phase of the catalytic process, the acyl-enzyme complex is cleaved in a de acylation step. Structural comparison of different Ntn-hydrolases shows that this mechanism is very similar with small variations in substrate binding and oxyanion hole. In relation to quorum sensing, it has been identified that the process goes through, in addition to hydrolases, which mostly contain cysteine in the N-terminal residues, the activation of enzymatic processes such as the Cysteine synthase, which appears to be an excellent target for inhibition in bacteria using chlorine dioxide.

Cysteine is an essential amino acid that performs vital functions in the catalytic activity and structure of many proteins. Cysteine residues are required for essential and ubiquitous proteins with iron-sulfur (Fe-S) clusters, including cytochromes and aconitase. Cysteine-derived proteins such as thioredoxin or thiols such as glutathione play a central role in protecting cells against oxidative stress. As a result of its crucial role in cell physiology and SH group reactivity, cysteine metabolism is tightly controlled in response to environmental variations. There are two main pathways of cysteine biosynthesis in microorganisms: the thiolation pathway, which requires sulfide and the reverse trans sulfuration pathway, which converts homocysteine to cysteine *via* a cystathionine intermediate (Figure 3). These pathways are only present in microorganisms such as bacteria and parasites and organisms such as plants and fungi; in humans there is no homologue of this enzyme and the synthesis of cysteine is carried out by another mechanism.

As for the most relevant pathway in this chlorine dioxide investigation, since it is only found in bacteria and parasites, it is the *de novo* pathway and comprises two parts: it begins with Serine Acetyl Transferase (SAT) to form O-Acetylserine (OAS) from L-serine and acetyl coenzyme A.

Subsequently, OAS reacts with sulfur to produce cysteine in an alanyl transfer reaction mediated by Cysteine Synthase (CS). OASS is a member of the cysteine synthase superfamily and is a Pyridoxal 5'-Phosphate (PLP)-dependent enzyme that exists in two isoforms: OASS-A and OASS- B. OAS is the preferred substrate for both isoforms, but while disulfide is the only sulfur source used by OASS-A, OASS-B can use both disulfide and thiosulfate.

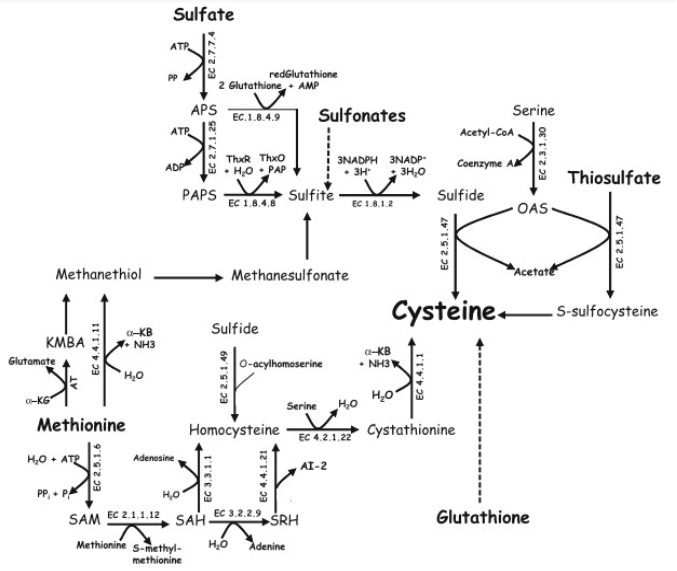

Figure 3. Pathways of biological synthesis of cysteine.

Undoubtedly, there is an important relationship between patient risk factors and the appearance of post-surgical infections; In general, the frequency varies between 1% and 15% of the cases, with a greater increase as the patient's risk factor increases [5]. The present investigation is very important since it is the first structured report of a series of cases of topical use of chlorine dioxide in the treatment of ulcers, wounds and infected burns worldwide, the result of which contributes to an effective solution, rapid and economical in these treatments compared to the usual treatments and above all, chlorine dioxide is revealed as the best substance to treat the great problem of infected wounds that is biofilm.

What is chlorine dioxide?

Chlorine dioxide is a molecule made up of one chlorine atom and two oxygen atoms [6]. Below 52 degrees Fahrenheit, chlorine dioxide is a liquid and above 52 degrees Fahrenheit it becomes a gas [7]. Chlorine dioxide is very soluble in water and when exposed to sunlight, it breaks down quickly [8]. First discovered by Sir Humphrey Davy in 18149, chlorine dioxide turned out to be a powerful oxidant because it has an unpaired electron in its outermost molecular orbital [10]. This strong oxidizing potential has given rise to a wide variety of applications in a multitude of industries [11].

Chlorine dioxide uses

Products containing chlorine dioxide are used as disinfectants and sanitizers in concentrations up to 6,000 ppm. The Environmental Protection Agency (EPA) first registered the aqueous form of chlorine dioxide for use as a disinfectant and sanitizer in 1967 and as a sterilant in 1988 [12].

Chlorine dioxide is also used as a water purifying agent. In Europe, this application began in the mid-19th century [13]. In the US, the EPA has approved chlorine dioxide to purify drinking water [14]. The Niagara Falls Water Treatment Plant in New York was the first municipal water treatment facility in the entire US to use chlorine dioxide in 1944. In the 1950s, chlorine dioxide began to replace chlorine in water treatment plants due to its superior ability to reduce unpleasant tastes and odors in drinking water, along with its effectiveness in destroying viruses, bacteria and other harmful microorganisms without forming trihalomethanes, which are a by-product of disinfection with chlorine [14,15]. Chlorine dioxide is currently used in approximately 5% of large water treatment facilities in the US to purify water [15,16]. This includes more than 500 public water treatment plants that use chlorine dioxide at full time and up to 900 who use it part time or seasonally [17,18].

In addition to water purification, other applications for chlorine dioxide include its use in agricultural, commercial, medical, industrial and residential sectors. The medical sector uses chlorine dioxide to sterilize equipment [19].

Chlorine dioxide has been registered by the EPA as a pesticide (i.e, antimicrobial) for its ability to kill microorganisms such as bacteria, viruses and parasites in surface waters, rendering them unfit for human and animal consumption [19]. Due to its safety, environmental friendliness, affordability and ability to destroy a wide range of microorganisms, chlorine dioxide has been called the "ideal biocide" [20].

Comparing the oxidizing power and the oxidizing capacity of different disinfectants, it is concluded that chlorine dioxide is effective at low concentrations. Chlorine dioxide is not as reactive as ozone or chlorine and only reacts with sulfuric substances, amines and other reactive organic substances. Compared to chlorine and ozone, less chlorine dioxide is required to obtain an effective residual disinfectant concentration. It can also be used when the concentration of organic matter is high [21].

Substances of an organic nature in bacteria react with chlorine dioxide, causing the interruption of different cellular processes. Chlorine dioxide reacts directly with amino acids and RNA in the cell. Chlorine dioxide attacks the cell structure or the acids inside the cell. Avoid the formation of proteins. Chlorine dioxide affects the cell membrane, denatures membrane proteins and fats and interferes with reproduction. It acts in particular on the amino acids cysteine, tryptophan and tyrosine [22].

The cellular immune system, specifically white blood cells, use

mechanisms for the generation of highly reactive oxygen derivatives called free radicals, through which it produces different oxidative-type processes that favor the activity of phagocytic cells, in order to combat the invasion of foreign organisms. Without these protective mechanisms provided by the immune system that involve oxygen derivatives, the ability to fight infections is impaired.

The immune system of many people, particularly in the elderly group, is deficient in the ability to provide these highly reactive oxygen derivatives (free radicals) so necessary to attack the wide variety of viruses as well as bacterial invaders that become in generator of many diseases; cultures of many bacteria become acidic, typically with lactic, acetic and other simple (organic) carboxylic acids. The acidic (protonated) environment that surrounds many bacteria triggers the oxidation that produces chlorine dioxide [22]. Oxygen is a particularly potent oxidizing agent for anaerobic organisms because it is essentially a free radical seeking not one but two electrons. Due to their low tolerance to oxygen and the acid environment in which they thrive (due to the release of organic acids), fungi in the form of mycelium are sensitive to the destructive action of chlorine dioxide. An example of pathogenic fungi in humans is *C. albicans*, which affects the dermis, skin and vagina, as well as Trichophyton, which produces ringworm or "athlete's foot", which generates mycotoxins that affect homeostasis.

Chlorine dioxide has shown a significant contribution to wound healing, infection prevention and tissue repair in ulcers and skin lesions through treatments based on a chlorine dioxide solution, with particular applications in ulcers and burns [23]. Additionally, preliminary research carried out at universities in Switzerland reveals a profound regenerative effect of chlorine dioxide on skin cell cultures because it increases and improves wound healing. The proposed mechanism seems to be the following nucleic acids (RNA and DNA) are made up of four base units linked in a chain. One of the basic units is designated as guanosine monophosphate or GMP. cGMP has been shown to stimulate cell division and is activated during the regeneration process. It is also known that the enzyme that synthesizes cGMP, guanylate cyclase, is stimulated by one of the highly reactive oxygen derivatives, the hydroxyl radical; symbolized by OH-. An oxidizing agent chemically similar to chlorine dioxide is periodic acid, HIO_4; in which four oxygen atoms are attached to a single halogen atom, iodine. In chlorine dioxide two oxygen atoms are attached to the chlorine halogen. It has been determined that the hydroxyl radical is present in solutions of periodic acid and by inference; it may also be present in solutions of chlorine dioxide.

Material and Methods

This is a prospective descriptive observational study in which a sample of fifteen adult hospitalized patients was taken, without risk factors, which had undergone surgical procedures without evidence of postoperative complications, belonging to patients in hospital beds of various ages. services, all under management by plastic surgery and the burn unit of the Reina Catalina clinic in Barranquilla in which, prior to grafting or performing any other reconstructive management, a sample was taken from the wounds with granulation tissue in patients with burns and ulcerative wounds, performing the collection strictly and carefully, avoiding sample contamination. All patients, fifteen in total, had preoperative infections.

In the initial stage of the literature search, the Search strategies in PubMed were as follows in summary: "Wound Infection"[Mesh] AND "Biofilms"[Mesh] AND "Chronic Disease"[Mesh])+Filter: Article type: review; Year of publication: 10 years; Species: Humans; Language: English and Spanish. =total of 16 items; "Biofilms/drug effects"[Mesh] OR "Biofilms/growth and development"[Mesh])) AND "Wound Healing"[Mesh]) AND "Anti-Bacterial Agents"[Mesh]+Filter: Article Type: Clinical Trial and review; Year of publication: 10 years; Species: Humans; Language: English and Spanish. =18 items.

The chlorine dioxide solution used is capable of reducing at least approximately five logarithmic scales in the concentration of samples of live microorganisms such as *P. aeruginosa, E. coli, E. hirae, A. baumannii, A. species, B. fragilis, E. aerogenes, E. faecalis,* Vancomycin-resistant *E. faecium (VRE, MDR), H. influenzae, K. oxytoca, K. pneumoniae, M. luteus, P. mirabilis, S. marcescens, S. aureus, S. epidermidis, Staphylococcus haemolyticus, S. hominis, S. saprophyticus, S. pneumoniae, S. pyogenes, C. albicans and C. tropicalis*, within 30 seconds after exposure of the microorganism to chlorine dioxide [24].

The administered solution can reduce a sample of live microorganisms, including *E. coli*, *P. aeruginosa*, *S. aureus* and *C. albicans* from an initial concentration of between about 1 × 106 and about 1 × 108 organisms/mL to a final concentration of about zero organisms/ml within approximately one minute of exposure. This corresponds to a reduction of ten logarithmic scales to approximately eight logarithmic scales in the concentration of the microorganism [24].

Procedure

To eradicate the biofilm, it is essential to break the slime layer present in the lesion and be able to expose the germs to the action of topical anti-microbial. In the cleaning process they went the following phases:

1. Cleaning of the wound and skin to remove devitalized tissue and residual elements of the biofilm. Chlorine dioxide associated with saline was always used.

2. Debridement, removing necrotic tissue, slough, residual elements and biofilm at each dressing change.

3. Conditioning of the edges of the wound, removing necrotic edges, scabs and protrusions that could contain biofilm to promote epithelial advancement and wound contraction.

4. Application of dressings to delay the formation of biofilm, these contain antibiofilm agents such as chlorine dioxide. These dressings control the humidity of the wound bed as well as protect from external factors that may delay healing.

In each patient, the tissue culture sample was taken with a scalpel; Colony-Forming Units (CFU) were determined in each sample, all giving a positive report for microbial agents. In these patients, a washing protocol was started in which a solution composed of 1000 cc of 0.9% saline solution and 10 cc of chlorine dioxide at 3000 ppm was used.

The solution was prepared with an ultrapure chlorine dioxide generator (Medalab, Health System) by application of a calibrated current to a sodium chlorite solution and osmotic water. This process is known as electrolysis and manages to separate the molecules of chlorine dioxide once the two components have been combined. When the current separates the oxygen molecules, they are free to adhere to those of Chlorine and obtain chlorine dioxide from highest purity, with a concentration of 3000 ppm. Surgical scrubs were performed prior to taking samples for culture obtained by smooth scraping with a scalpel, taking sterile gauze soaked in isotonic solution and cleaning the wound with sustained pressure. The gauze in a container with a red bag was discarded and the procedure was repeated until the wound appeared clean. Washes were performed with the chlorine dioxide solution, cleaning the wound with rotary movements, leaving the solution to act for three minutes, covering with sterile compresses. Daily surgical scrubs were performed in all patients. A maximum of 24 hours after the third day of washing, a sample was taken from the treated wounds to perform a control culture. We wash for three days intraoperatively and/or with other patients outside the operating room. After three days we made an appointment for a fourth day in the operating room for a new culture sample.

Results

In the group of patients, in the first sampling for cultures, multiple microorganisms were isolated, which were quantified through tissue cultures taken with a scalpel intraoperatively. The results of the cultures were:

1. 6 patients (40%) *P. aeruginosa*.

2. 3 patients (20%) *P. mirabilis*.

3. 3 patients (20%) *E. cloacae*.

4. 3 patients (20%) *E. coli*.

Tissue culture revealed that the Colony-Forming Units (CFU) of said cultures were between 103-106; Immediately after obtaining the result of the first culture, the topical CDS protocol was started with the purpose of exploring this new therapeutic option to free the tissues from the presence of bacterial and fungal microorganisms (Table 2).

In each patient, three surgical washes were performed with 1000 cc of 0.9% saline solution plus 10 cc of chlorine dioxide at 3000 ppm. At the end of the third day of surgical washings, a control culture was taken again. Obtaining as a final result negative cultures in all patients after 72 hours of incubation (Figures 4-8).

Discussion

In patients normally treated in plastic surgery, the presence of infections by microorganisms that delay healing time and lengthen the hospital stay is very frequent, since topical management is difficult to completely eliminate these agents; that motivated us to look for a new option to existing treatments. Using translational medicine criteria, we transferred water-solubilized Chlorine Dioxide (CDS) from its use as a disinfectant on surfaces, where it is considered the best existing biocide, to its use as a disinfectant for wounds, ulcers and infected burns in humans; based on previous research, we established the topical CDS protocol for the treatment of IPPB.

Chlorine dioxide should be considered as a bactericidal agent; it has the possibility of becoming a commonly used antiseptic to treat properly infected wounds. Through the procedures that we carried out to verify the bactericidal efficacy of chlorine dioxide, a positive response was evidenced in one hundred percent (100%) of the cases after washing the wounds.

Table 2. Pathogens from a sample of 15 patients before carrying out the washing protocol.

Pathogens	No. of Patients
P. aeruginosa	6 patients
P. mirabilis	3 patients
E. cloacae	3 patients
E. coli	3 patients
Total	15 patients

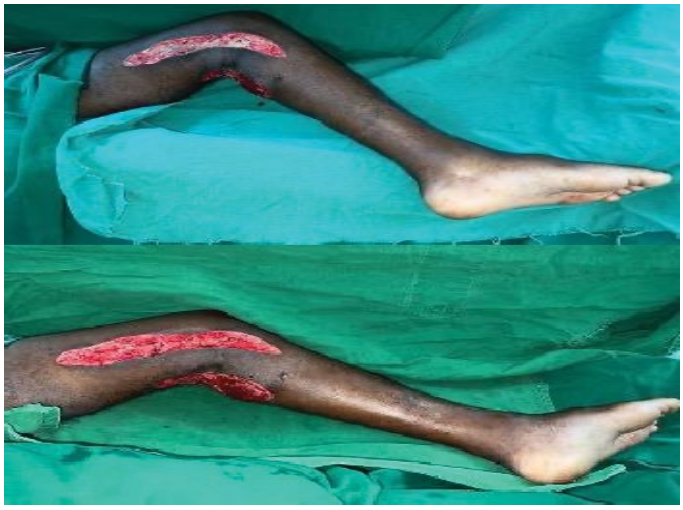

Figure 4. Patient with a gunshot wound before the first wash and on the fourth day of washes.

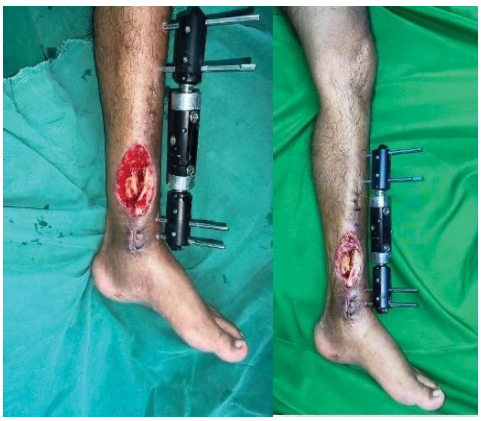

Figure 5. Patient before and after four days of washing.

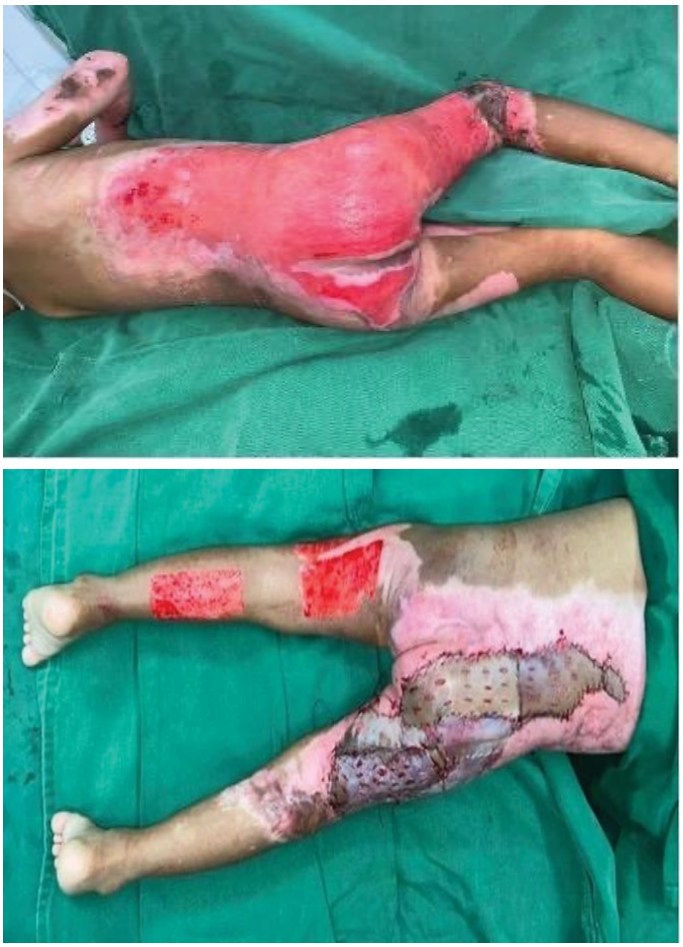

Figure 6. Patient with burn before and after four days of washing.

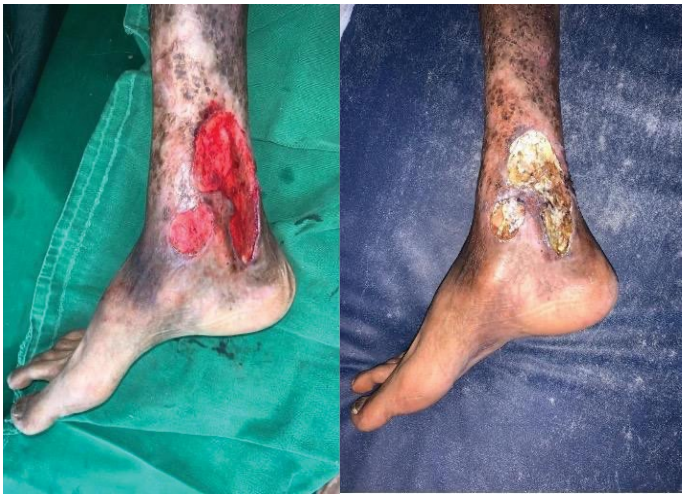

Figure 7. Patient with diabetic ulcer before and after four days of washing.

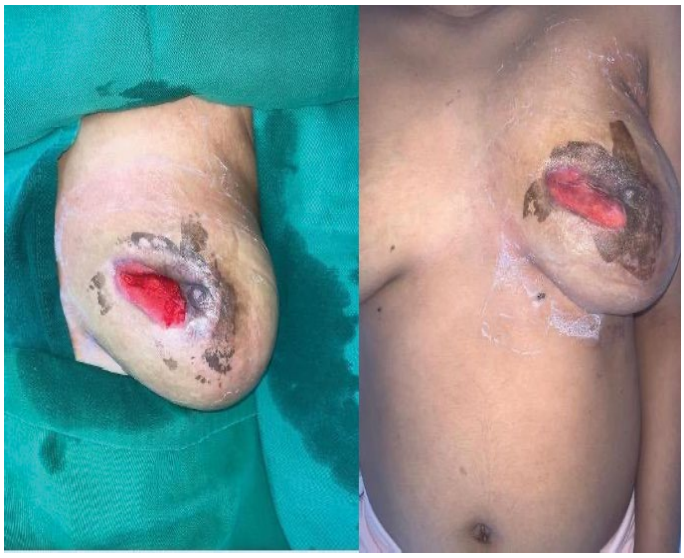

Figure 8. Patient with post-infectious ulcer before and after four days of washing.

Substances of an organic nature in cells of bacteria react with chlorine dioxide, causing the interruption of different cellular processes. Chlorine dioxide reacts directly with amino acids and RNA in the cell, attacking the cell structure or the acids inside the cell and preventing the formation of proteins [25,26].

Chlorine dioxide is a size-selective antimicrobial agent that can kill micron-sized organisms quickly, but cannot cause real harm to much larger organisms, such as animals or humans, since it cannot penetrate deep into their living tissues [27]. In addition, the circulation of multicellular organisms may provide additional protection for these organisms against ClO_2. In free aqueous solutions, the most potent chemical disinfectant is ozone. However, in biofilms, ozone performance is quite poor. Furthermore, ozone is toxic and decomposes rapidly in aqueous solutions. (Its half-life is only 15 minutes at 25°C and pH 7). These (disadvantageous) properties of ozone do not allow its use as an antiseptic in most applications [27]. The second most powerful disinfectant after ozone is chlorine dioxide [28,29]. A comparative test of eleven disinfectants in three organisms; two bacteria, *S. aureus, P. aeruginosa* and yeast, *S. cerevisiae*. Tanner found that the disinfectant containing chlorine dioxide had the highest biocidal activity on a mg/L basis against the organisms tested. An additional and very important advantage is that chlorine dioxide can quickly remove biofilms or biofilms [30] because it is highly soluble in water and, unlike ozone, does not react with the extracellular polysaccharides of the biofilm. Thus, chlorine dioxide can rapidly penetrate biofilms to reach and kill microbes living within the film, making bacterial resistance to chlorine dioxide theoretically impossible.

Chlorine dioxide is a strong oxidizer, but quite selective. Unlike other oxidants, it does not react with most organic compounds in living tissue. However, chlorine dioxide reacts fairly quickly with cysteine, methionine (two sulfur-containing amino acids), tyrosine and tryptophan [22]. The interesting thing about our research is that using several hypotheses based on the infection process and biofilm generation, it is possible to explain that, among other possible explanations, through the inhibition of the Cysteine Synthase as target, Chlorine dioxide becomes an excellent therapeutic tool for the inhibition of bacteria and, in particular, the prevention and dissolution of biofilm.

Conclusion

After analyzing the results obtained, we can classify chlorine dioxide as a bactericidal agent with a local effect that shows safety and efficacy because it acts locally and does not delay the healing process, that is, it is not cytotoxic but quite the opposite, it promotes the wound healing. It shows efficacy in relatively low concentrations and microbes do not develop resistance against it, which explains the therapeutic result of 100% success in the treatment of infected wounds, ulcers and burns. This is a preliminary study and the results of this article yielded important conclusions that encourage further studies, hopefully randomized double-blind, to demonstrate the efficacy of chlorine dioxide in the health area [31] and especially its use as the most effective bactericide for use on infected wounds, ulcers and burns, dissolving the biggest problem of skin and soft tissue infections such as biofilm.

Conflict of Interest

The authors declare no conflict of interest or no competing economic interests. Authors have completed the ICMJE conflict of interest declaration form, translated into Spanish by Medwave and declare that they have not received funding for the article/research; have no financial relationships with organizations that could have an interest in the article published in the last three years; and have no other relationships or activities that could influence the published article. Forms can be requested by contacting the responsible author. This does not alter the authors' adherence to all policies on the exchange of data and materials.

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