A narrative review on the use of hypochlorous acid in dentistry

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Abstract

Hypochlorous acid is the most effective disinfectant in the chlorine family available in dilute solution. The present narrative review investigates the advantages of using Hypoclorous acid for the disinfection of dental setting, aiming to reduce the risk of contamination and cross infections. The use of HOCl has been also investigated during the pandemic period of Covid-19 and possible usage of this well-known disinfectant as valuable device for virus charge reduction is described.
HOCl is considered useful in the disinfection of water lines, surfaces and dental devices, and also to reduce the risk of airborne infections if sprayed in the environment of the dental setting, especially when the target is a capsized virus.
HOCl is characterized by reasonably low costs, easy management and multiple purposes that could encourage dentists to incorporate the use of novel hypochlorous acid solutions, hydrogels or sprays in their practice. Since there are many possible uses of HOCl in dentistry, further investigations are necessary to comprehend and evaluate the effectiveness of HOCl in the different dental office's situations and settings.

Keywords: Early Childhood Caries, Children, Risk Assessment, Socio-demographic Factors.

Introduction

Hypochlorous Acid (HOCl) is a biologically occurring chemical that is produced in human bodies by neutrophils and monocytes: myeloperoxidase living in the mitochondria of these cells is the catalyst for converting chloride ions (Cl^-) and hydrogen peroxide (H_2O_2) into HOCl. Endogenous HOCl can be produced as a normal by-product of aerobic metabolism, and during infections and inflammation processes. HOCl provides a unique power in cell defense against pathogens, while not harming our cells. Detection of HOCl in activated phagocytes is critical since they mediate in a variety of cellular processes such as signaling and immune response, as well as oxidative damage of key biomolecular systems (1). HOCl was discovered in 1834 by the French chemist A.J. Balard by adding, to a flask of chlorine gas, a dilute suspension of mercury oxide in water. When chlorine dissolves in water, it can give both hydrochloric acid (HCl) and hypochlorous acid (HOCl). The latter itself is a stronger oxidant than chlorine under standard conditions, reacting with a wide variety of biomolecules, including DNA, RNA, fatty acid groups, cholesterol and proteins. HOCL has the same active ingredient of household bleaches and disinfectants, like sodium hypochlorite (NaClO) and calcium hypochlorite ($Ca(ClO)_2$) but with a different chemical structure, and consequently different characteristics, both in terms of efficiency and safety: NaClO is commonly used in concentrations that range from 1% to 5%, that could be dangerous if inadvertently

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get in contact with eyes, resulting in chemical burns. On the contrary, HOCl is generally used in much lower concentrations, avoiding the above-mentioned risks.
Hypochlorous acid is the most effective disinfectant in the chlorine family available in dilute solution. Studies have been shown that antibacterial activity of HOCl can be up to 120 times higher than NaClO, being also much more effective on biofilm eradication (2-4). Such an improved disinfectant action is related to the following factors: HOCl has no charge and has a relatively low molecular weigth. Therefore, it has superior capability to penetrate the cell walls, in comparison to sodium hypochlorite and other chlorine-based disinfectants (ie. sodium hypochlorite). Moreover, oxidation reactions with organic matter, which are the critical components of microbial cells, is more rapid and intense. On the contrary, the negatively charged hypochlorite ions cannot diffuse through the cell wall, because they are electrostatically repelled from the negatively charged cell walls. In addition, being much larger in size than a HOCl molecule, the hypoclorite ions diffuses more slowly through the cell walls, due to the above-mentioned factors, sodium hypochlorite is a relatively poorer disinfectant when compared to HOCl.
HOCl solutions have been used for over 100 years, in the early 1900's during the World Wars, HOCl solutions were used for disinfecting medical equipment and dressing wounds. Unfortunately, its use was eclipsed by two factors: the widespread introduction of antibiotics and its lack of shelf stability. However, in recent years questions have been arised concerning antibiotic resistance and cytotoxicity of antiseptics, and their impact in wound care practice, and consequently, more attention was paid to find alternative therapeutic agents, including more advanced HOCl solutions (5).
In the last decade, new HOCl solutions have been developed and commercialized, mainly to overcome the lack of shelf stability, which had been an overwhelming impediment to its widespread use (6); although producing HOCl solutions is not challenging, stabilizing the solution is very difficult. Until now, HOCl solutions would only remain stable for about a few hours or even less before turning back into salt water, therefore being not suitable for use in pharmaceutical or healthcare environments. Nowadays, improvements in chlorine chemistry currently allow to produce stabilizds HOCl solutions with a shelf life of 18 months.
HOCl is one of the only agents that is both non-toxic to the cells and can heal wounds while being lethal to almost all known dangerous bacteria and viruses that threaten our health (7). HOCl exerts a rapid and selective inhibition on RNA synthesis as well as DNA synthesis, and this may disrupt membrane/DNA interactions which are needed for replication. HOCl alters the DNA template itself, inactivates enzymes of the replication system and inhibits synthesis of critical proteins required for DNA replication and/or cell division (8).
HOCl is actually approved by the Food and Drugs Administration of United States of America for use in wound healing, wound care and eye care products. Studies have shown its potential as a nasal irrigation solution to fight influence virus. It's also FDA approved for use in products preservation and the United States Department of Agriculture approved it for organic crop preservation.

The aim of this review was to enlighten the many possible uses of HOCl in dental enviroments and procedures, and, more specifically, HOCl possible applications in the control of COVID-19 infection in dentistry.

Use of hypochlorous acid in dentistry.

There are many possible uses of HOCl in dental enviroments and procedures. In the first case it can be used for water line disinfection, environmental surface disinfection, and as hand sanitizer; in the second case it has been proposed as mouth rinse, as an endodontic irrigating solution, as a dentine conditioner and in the treatment of perimplantitis. Benefits of HOCl in these application will be therefore discussed.

Water line disinfection.

In a dental unit, differences in thickness and construction materials can facilitate the contamination of the water lines with environmental microorganisms, pathogens and opportunistic pathogens. Water is usually provided by a self-contained water reservoir or by municipal supply: even if the municipal water entering in the dental office usually contains a minimal concentration of waterborne bacteria and a small amount of nutrients for their growth, during dental treatments, some microorganisms can adhere to the internal surfaces of the lines and form biofilms. This may lead to a possible waterborne infections or airborne contamination when using aerosol-producing devices, like high-speed handpieces and ultrasonic scalers (9,10).
Proper application of chlorine will produce microorganisms-free water and eliminate algae and slime in many fields: drinking water, industrial processing waters (bottling and canning), cooling tower systems, drip irrigation systems, sanitary sewage, processing wastewater, swimming pools, etc. Ideally these processes should be relatively simple, with reasonable costs, non-toxic, not damaging systems, avoiding fire hazard. The weak HOCl acid, derived from adding chlorine (as a granular powder, liquid or sometimes in its elemental form as a gas) to water, is widely used for these applications since it shows most, if not all, the above-mentioned properties. It is very proficient at killing bacteria such as salmonella and Escherichia coli, and it also kills many viruses. By easily penetrating microorganisms' cell walls as previously described, the hypochlorous acid chemically interacts with proteins, causing them to lose their complex, origami-like structures. The proteins' functionality deteriorates, and the microorganisms start to die. Similarly, antivirus property has been demonstrated (11,12). Only few microorganisms, more specifically diarrhea-inducing protozoa like Giardia Lambia and Cryptosporidium, are very resistant, because they have strong protective outer shells, and this may allow possible waterborne transmission.
To let the chlorine to properly work against susceptible pathogens, the pH of the water must be maintained within a certain range. Ideally, chlorine concentration should range between one and three parts per million and the pH of the water should range between 7.2 and 7.8. Luckily, in a dental unit these parameters can be easily controlled, by using very precisely diluted concentrations with a stable pH in a self-contained

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water reservoir. In the above-mentioned concentration and pH neutral ranges, approximately 76% of the chlorine is in solution as HOCl, which is not damaging dental lines, being not highly corrosive. Moreover, differently from NaOCl there is minimal risk of salt precipitation that can obstruct very small water lines. Commercial solutions could be provided ready to use; improvements in the chemical stabilization allowed careful bottling and made this product available across the world, with ideal concentrations and pH for the specific use. As an alternative, HOCl could be also prepared by adding specific chlorine tablets in the dental unit water reservoirs. Commercial products are user-friendly, having the capability of being used in the environment without causing any harm to the users and the environment.

Enviromental surface disinfection

Routine disinfection (daily and at patient discharge) and cleaning of environmental surfaces in dental facilities is a fundamental tool in preventing airborne or blood-transmitted infection. Because many factors make it difficult to achieve high rates of effective disinfection on a routine and sustained basis, continued efforts to improve the quality and consistency of traditional cleaning and disinfection practices and products are needed. The use of new HOCL-based products is one of these options, since several studies demonstrated that stabilized HOCl exhibits rapid, concentration-dependent activity against a wide variety of gram-negative and gram-positive bacteria, viruses, and fungal pathogens, as long as the narrow effective pH range is maintained (13-16). Improvements in chemistry resulted in new hydrogel products, with a longer shelf life, and predictable activity, which can be used as wound cleaners, first aid solutions, hand sanitizer and surface cleaners. Commercial HOCl hydrogels can exhibit different viscosity and consequently be used with dispensers or sprays.

During dental treatments dentists and staff use gloves which can become contaminated; special care must be paid to avoid unnecessary touching of surfaces and to cover (and then disinfect) the ones which are used with disposable plastic protection. HOCl kills bacteria and viruses as effectively as bleach, but with no harmful residues left behind, and no allergens or irritants. Therefore, it is used as a disinfectant also in hospitals, veterinary offices, schools, etc. (17-18). It was found to be helpful in eradicating biofilm which can be seen (i.e. in sink and floor drains often appearing as slime and discoloring) or cannot (i.e. air handlers, air conditioning evaporation trays, water cooling towers). Moreover, despite standardized processes thought to be effective at sterilizing medical instruments, biofilm is highly dangerous, being often very pervasive and robust; thinking that pouring a bleach solution down a drain or on a surface will solve the problem is a wrong belief. Bacteria create biofilm to protect themselves from harsh environments, including disinfectant agents; indeed, bacteria in biofilms can be even 1000 times more resistant than in a planktonic form. It has been shown biofilm, which had not been eradicated and removed during reprocessing of instruments prior to surgical procedures, resulted in infections being transferred to patients (19).

Hypochlorous acid is currently registered at the Environmental Protection Agency (EPA) as a hospital-grade disinfectant that is as effective as bleach (if not more) in the biofilm-abolition process and is much safer for the environment, metals, staff and PPE, especially in closed and fresh-air-deprived environment (14). Odor is well tolerated, and no relevant toxic/allergenic reactions are documented. In dental offices HOCl solutions and hydrogels are usually applied by scrubbing or high-pressure spraying; manufacturers' instruction should be followed and be appropriate to the environment and conditions. HOCl is a fast-acting agent: it rapidly kills microorganisms, hence reducing the duration of their potential contact with patients and health care professionals. In a study on surfaces near patients, it showed highly significant reduction of bacterial levels when compared to a quaternary ammonium disinfectant. Authors reported that spraying procedure was simple and rapid, requiring only approximately 15 s per application, and the product could be left to dry without wiping. (20). In dental offices cleaning and disinfection of all areas is needed, including the radiology and laboratory areas, where costly devices must be also properly sanitized avoiding any damage. HOCl can be used on most surfaces and instruments without corroding them or damaging their structural integrity (16,21).

Hand, wound sanitizers and other uses in healthcare

Personal hand hygiene is also paramount in the prevention and transmission of diseases (22). HOCl also fits into the requirements for hand and wound sanitizers: it has broad-spectrum efficacy, is odorless, fast drying, non-toxic or allergenic. HOCl hydrogels as hand sanitizers are efficient and safe, containing no alcohol and do not require rinsing after use.

Several studies have validated the use of ordinary HOCl anti-infective sprays in patients (often diabetic) with open wounds. Clinical reports showed HOCl to be effective, to improve healing by increasing oxygenation of the wound, and to be safe, without adverse effects in the wound healing process. In addition to its antimicrobial activity, HOCl was found helpful in removing strong odors from the wounds and in reducing patients' discomfort by providing a cooling sensation on the wound itself. (23,24) In terms of promoving the healing process, stabilized HOCl solutions were found to have dose-dependent favorable effects on fibroblast and keratinocyte migration, significantly higher than other medicaments (povidone iodine and media alone). HOCl also showed a potential for reducing scarring when combined with silicone (25).

Additionally, antiseptic skin preparation containing HOCl, did not produce any ocular toxicity or ototoxicity, while some concerns were raised on the use of chlorhexidine based products. In terms of eye care, HOCl products were found helpful in providing effective relief from dry eyes and hordeola. They can be also a therapeutic option for red, itchy eyelids associated with conditions such as blepharitis and meibomian gland dysfunction (26). Indeed, HOCl-containing lid hygiene products for daily wellness routine have been recently commercialized, to decrease the microbial load on the lids and lashes.

Concerning infections of the nasal respiratory tract, low concentrations of HOCl have shown both antibacterial and antiflu virus activity, but no product has been commercialized to date against human rhinovirus (HRV). In experimental studies, however, HOCl treatment significantly inhibited HRV-induced secretion of IL-6 and IL-8 and significantly reduced viral titer. The effects of HOCl peaked at 1 minute after HOCl generation and decreased thereafter, suggesting a possible future therapeutic use (27).

Uses in dental care

HOCl antiseptic was found to be effective for cleaning biofilm-contaminated implant surfaces. Periimplantitis are very complex infections and difficult to eliminate because the initial bacterial adhesion and biofilm formation starts in areas of high wettability (inside the pits and grooves of the roughened implant surfaces) which are difficult to reach and disrupt by routine dental hygiene (28). Due to its high non-specific antimicrobial activity and efficacy on biofilm, HOCl solution have been suggested in dental treatment procedures, but to date just a few researches or clinical reports are present in the dental literature. A mild acidic HOCl solution was proposed as an endodontic irrigating solution, but it was found to be less effective than sodium hypochlorite in eliminating pulp soft tissue (29).
HOCL was also proposed as a chemotherapeutic agent for the treatment of periodontitis (30). When compared to chlorhexidine, it proved to be effective, with less side effects, but without substantivity. Therefore, its overall antibacterial effect was reduced, being not as persistent as chlorhexidine (31).
In restorative dentistry studies have shown that smear layer deproteinization with HOCl solutions enhanced the dentin bonding (32). Same results were obtained in another research, where smear layer deproteinizing was carried out by the application of 50ppm hypochlorous acid on dentin surface for 15s followed by p-toluenesulfinic acid salt for 5s prior to adhesive application (33).

Possible uses of HOCl in improving covid-19 infection control in dentistry

The outbreak of Coronavirus (COVID-19), first in Asia and Europe, and subsequently in the US and worldwide, followed by pervasive measures implemented by governments to limit the virus transmission, also concerning the reduction of dental treatments and the closure of dental offices. The main transmission route of COVID-19 was found to be through airborne droplets, touching or encountering an infected person or a contaminated surface. In addition, COVID-19 was found in the saliva, increasing concern in the public opinion on the transmission for COVID-19 in the dental setting. The New York Times listed the dentists and their staff as the workers who face the highest COVID-19 risk, since they can encounter COVID-19 infection daily and typically work near one another and their patients. Due to the unique characteristics of dental procedures where many droplets and aerosols could be generated, the standard protective measures in daily clinical work could not be effective enough to prevent the spread of COVID-19, especially when patients are in the incubation period, are unaware that they are infected or choose to conceal their infection. Therefore, the scientific community and national governments provided practical recommendations to refine preventive strategies to avoid the COVID-19 infection by focusing on patient placement, hand hygiene, enviromental disinfection procedures and personal protective equipment (PPE).
Hand hygiene has been considered the most critical measure for reducing the risk of transmitting microorganism to patients (34). Hand sanitizers were found to be more effective than plain soap and water in preventing transmission of bacteria from the hands of individuals, and consequently could be an adjunct or effective alternative to hand washing to achieve asepsis in routine clinical practice (35). Many hand sanitizers are available in the market with varying degree of effectiveness. Alcohol-based hand sanitizers are the most used products: ethyl alcohol (70%) was found more effective compared to isopropyl alcohol. Unfortunately, some products marketed to the public, despite a label claim of reducing "germs and harmful bacteria" by 99.9%, were not found to be so effective in reducing bacterial counts on hands (36).
In COVID-19 times in many health care-environments, including dental settings, besides the traditional use of gloves for practitioners and assistants, the use of hand sanitizers will probably become a mandatory/strongly recommended prevention measure. All patients had to disinfect hands immediately after entering the dental office, and all the staff will have to do same very often during the working hours to reduce the risk of cross infections.
COVID-19 fueled research towards more efficient and user-friendly hand sanitizers, due to their predictable extended usage in routine work. Hand sanitizers with alcohol are currently used in many medical/dental offices, but over time repeated use may lead to allergic reactions and hand dermatitis. Fortunately, non-sticky, quick drying, rinse free, HOCl hydrogels and sprays with no toxic or irritating side effects, can prove an instant antimicrobial effect more powerful than alcohol alone. Some of these sprays, being multi-purpose sanitizers, could also be used as air sanitizer. On the contrary, the use of HOCl solutions as mouthrinse before treating patients cannot be advocated, since the antiseptic activity is less persistant than clorexidine (31).
Coronaviruses, as with Hepatitis, flu, Herpes, etc. are enveloped viruses. Enveloped viruses are viruses that possess an envelope or outer coating that is composed of a lipid layer (fat-like substance that is water insoluble) and is needed to aid the attachment of the virus to the host cell. Chlorine-based disinfectants (and particularly HOCl, due to its unique characteristics of penetrating cell walls) are capable to easily disrupt such lipid-layers, causing loss of the envelope and consequently loss of infectivity. To date, no commercially available disinfectant has been specifically tested against COVID-19; however HOCl was found to be highly efficacious against a wide range of microorganisms including other both enveloped and non-enveloped viruses similar to COVID-19 (Norovirus and Rhinovirus type 16) leading to the reasonable conclusion that it will be highly effective (11,12,14,15,27).
According to various studies, viruses like SARS-CoV-2, can persist on surfaces for a few hours or up to several days, depending on the type of surface, the temperature or the humidity of the environment (37-39). There is currently no agreement if COVID-19 may have or not such a resistance. In any case,

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these data highlighted the importance of thorough disinfection of all surfaces within dental clinics. Every surface in the waiting, meeting and operative rooms must be considered at risk; therefore, in addition to providing increased periodic air exchange and more frequent sanitization of air conditioning, all surfaces, chairs, magazines and doors that come into contact with healthcare professionals and patients must be considered "potentially infected".

Therefore, in COVID-19 times more accurate and frequent environmental and surfaces procedure will be performed. Viruses can persist in the environment for days, but are relatively easy to kill, especially enveloped ones, by a wide range of disinfectants. Besides this, other properties will become important on an extended routine basis in a dental setting: costs, easy to use and lack of adverse effect, mainly concerning allergic and toxic reactions. Some gluteraldehydes need a long contact time (30 -60 minutes), which could limit their routine use on instruments and devices that are frequently used. HOCl is able to provide an excellent, significant viral reduction in less than a minute, which makes it effective in a spray and wipe cleaning regime on nearly all surfaces and devices present in a dental office. Moreover, many common disinfectants, such as glutaraldehyde, sodium hypochlorite, and chlorine gas, have been associated with occupational illnesses. Continuous exposure to glutaraldehyde may induce contact dermatitis in health workers; occupational asthma was reported in workers using routinely quaternary ammonium compounds (40,41). Environmental disinfecting devices using aerosolization requires the use of personal protective equipment and a self-contained breathing apparatus which makes the use of these devices more complex and costly. A significant advantage of HOCl is its lack of toxicity at ready-to-use concentrations: similarly, it is a non-allergenic product. If sprayed, only common, non-expensive surgical mask and glasses could be needed. The capability of a sprayer to make smaller particles was thought to help solution's molecules to be suspended in the air for a longer period of time (even if virus is usually inactivated within 5 seconds). Because of their low settling velocity rate, according to the authors, this increased the chance of HOCl to come in contact with the virus and kill it (10). Based on these findings, in COVID-19 time, dental assistants could spray almost continuosly HOCL particles around patient's mouth while aerosols producing procedures are being performed by the dentists. In such case patient's eyes should be preferably protected with glasses. Theoretically, this procedure could decrease the risk of airborne infection, in a simple and rapid way; the overall risk of surface /enviromnental contamination and direct human contamination through droplets and aerosols could be significantly reduced, even if some studies will be needed to verify such assumptions. In restorative and endodontics HOCl could be also directly sprayed on the external part of the rubber dam, including the tooth to be treated (32).

Potential risk of airborne and waterborne contamination could also be reduced by daily addiction of HOCl in dental unit water lines: such a simple procedure could be performed every morning (or every few hours if needed), ideally adding a properly stabilized commercial solution inside self-contained water reservoir, to ensure an increased antiviral activity not only towards the water lines and handpieces, but also towards the patient. When sprayed in patient's mouth this water may get in touch with virus in the saliva or in the patient's breath, and partially or significantly inactivate the virus. As previously stated, all these measures which seems to be easy to adopt, with reasonably low cost, and no side effects should be validated by future studies.

In COVID-19 times HOCl can also become the ideal product for the disinfection and decontamination of non-disposable personal protective equipment like glasses or protective transparent shields, which are continuosly wear by dentists and staff during clinical procedure and get in close contact with aerosols and droplets. Their disinfection must be simple, quick and efficient, non-irritating, and must leave no remnants on the surface: all these characteristics can be found in HOCl solutions or sprays.

Conclusions

The present review not only analyzed the possible advantages of the use of hypochlorous acid in dental settings, but also discussed how it could be beneficial when increased disinfection measures are adopetd to prevent COVID-19 infections. Reasonably low costs, improved effectiveness, easy applicability, multiple use and increased safety were found as the most useful points that could encourage dentists to incorporate the use of novel hypochlorous acid solutions, hydrogels or sprays in their practice. Moreover, few innovative solutions to reduce the risk of infections during aerosol producing procedures can be adopted, aiming at providing more safety without increasing the complexities of the procedures.

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