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Technical Paper

Antagonism between Chlorhexidine and Other Compounds of the Dentifrices - A Technical Note of the Products in US Market

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Abstract

Chlorhexidine is widely used and prescribed in management and control of the periodontal disease, and in the reduction of the oral pathogens previous or after the surgical procedures. However, few studies have been approached the antagonism between chlorhexidine and others compounds of the dentifrices. The purpose of this article is to present these possible antagonistic relationship between the chlorhexidine and others compounds of the dentifrices. When analyzing the instructions of use on such commercial products, it was found that there is little or no concern in emphasizing that use should be avoided right after tooth brushing. Thus, the dentist must have adequate knowledge when prescribing such antiseptics to ensure successful therapy with chlorhexidine in Dentistry.

Keywords: Chlorhexidine; Chlorhexidine/Antagonists and Inhibitors; Dental Plaque; Dentifrices; Periodontal Diseases

Technical Note

Chlorhexidine is a cationic antiseptic that has affinity for anionic surfaces, such as hydroxyapatite and dental biofilm [1-3]. This solution is widely used in Dentistry, due to its high substantivity and effectiveness [1-12]. However, few professionals are aware that the activity of this antiseptic can be neutralized by the action of other substances, due to antagonism between the components of mouthwashes and toothpastes.

Sheen., *et al.* [11] (2001) reported that the adsorption of antiseptics to tooth surfaces and the biofilm allows the exposure of cationic charges, making them susceptible to interactions with loads of phosphates and sulfates. However, since chlorhexidine is dicationic, susceptibility to interactions is potentially greater when compared, for example, to the load of cetylpyridinium chloride, which is monocationic. Nevertheless, independently of the ionic potential, it was demonstrated that the antiseptic concentrations of varying clinical concentrations of both chlorhexidine and cetylpyridinium chloride are altered by components of toothpastes.

Barkvoll., *et al.* [1] (1988) observed that the antimicrobial effect exerted by chlorhexidine is modified in the presence of sulfates and phosphates, due to the formation of insoluble salts that reduce the availability of chlorhexidine molecules and, therefore, their effectiveness. Accordingly, monofluorophosphate and sodium lauryl sulfate, anionic substances present in mouthwashes and toothpastes, may reduce the effect of chlorhexidine on the biofilm.

Owens., *et al.* [10] demonstrated that the use of toothpaste prior to rinsing with chlorhexidine significantly reduced its antimicrobial activity, when compared to the use of toothpaste after the mouthwash. As concentrations of monofluorophosphate and sodium lauryl sulfate are extremely high during the first minutes after brushing, reactions between the chlorhexidine and these sulfate and phosphate ions may occur and *in vivo* experiments have shown that this incompatibility is due to ionic interaction.

Barkvoll., *et al.* [2] analyzed the interference of sodium lauryl sulfate in the antimicrobial power of chlorhexidine, *in vivo*. Results showed that rinsing with chlorhexidine, subsequent to the use of sodium lauryl sulfate, played a smaller role in the formation of biofilms than the use of chlorhexidine alone. The intervals of 3 minutes, or even 30 minutes between the use of sodium lauryl sulfate and chlorhexidine, showed a reduced effect of the antimicrobial. In contrast, an interval of 2 hours resulted in a statistically similar action of the antiseptic on the biofilm to that found with chlorhexidine alone. One of the hypotheses was the formation of a salt with low solubility and low anti-bacterial power that would neutralize the effect of chlorhexidine.

Luoma., *et al.* [6] analyzing the influence of pH, demonstrated, *in vitro*, the synergistic effects of the simultaneous association of fluoride and chlorhexidine on the metabolism of *Streptococcus mutans*. A pH of 5.8 was found to be ideal for the simultaneous association to be effective, as the fluoride showed a greater inhibition of bacterial metabolism of potassium and phosphorus, as well as reducing acid synthesis of *Streptococcus mutans*. The action of chlorhexidine was considered satisfactory at this pH, although Hugo., *et al.* [4] reported that the effectiveness of chlorhexidine is greater at close to basic pH. Freitas., *et al.* [3] also studied such an association and suggested that the fluoride, present as molecules with low molecular weight, could reach locations inaccessible to chlorhexidine gluconate, helping to control plaque. In contrast, Melo., *et al.* [8] refuted such a hypothesis with evidence that the association decreased the concentration of chlorhexidine by ionic interactions and antagonistic competition for binding sites on the substrate. Therefore, this clinical correlation was not satisfactory for the control of periodontopathogenic microorganisms. Zickert., *et al.* [12] showed that the combination of fluoride and chlorhexidine may be of benefit in reducing the development of caries.

Using a mouthwash formulation containing both chlorhexidine and sodium fluoride in its composition, Jerkins., *et al.* [5] showed, through *in vivo* studies, that chlorhexidine may have a secondary effect to fluoride, and that this compound causes little or no interference in the activity expected for chlorhexidine alone. With regard to the role of fluorine in the de-/remineralization process, Luoma., *et al.* [7] showed, *in vitro*, that the effect of fluoride on the solubility of enamel is similar to the association of fluoride and chlorhexidine. There was a difference in the time required for the enamel to achieve a balance in the de-remineralization process, where the association was considered as minor in relation to fluoride alone. Thus, chlorhexidine may be used in combination with fluoride for the treatment of enamel with no significant interference in the protective action of fluoride. Analyzing the minimum time interval between brushing and rising with chlorhexidine, Barkvoll., *et al.* [1] concluded that a minimum of 30 minutes is enough to ensure a significant action of the two compounds (chlorhexidine and fluoride).

Rossi-Fedele., *et al.* [13] reviewed the possible interactions between chemical agents used as root canal irrigators during endodontic instrumentation and treatment: chlorhexidine, sodium hypochlorite, EDTA and citric acid. It was found the difficulty in obtaining a homogeneous solution between the association between chlorhexidine and EDTA, as they cause a precipitate and make its use unfeasible. Although the research includes only chemicals used in Endodontics, it is noteworthy that EDTA is one of the components of dentifrices and other mouthwashes, used as a chelating agent.

Scheibler., *et al.* [14] observed a reduction in efficacy and high percentages of degradation between nystatin and chlorhexidine when used in combination against *Candida albicans*. When isolated, they were more effective, respecting the 30-minute time between nystatin and chlorhexidine.

There are many products manufactured and commercialized in the US (Table 1), which contain chlorhexidine in their formulations. However, when analyzing the instructions on such products (in your labels), it was found that there is little or no concern in emphasizing that use should be avoided right after tooth brushing. This search was performed by consulting the dailymed website (dailymed.nlm.nih.gov), and selecting all trademarks for human use, containing only chlorhexidine gluconate 0.12%. Most labels indicate the use of mouthwash with 15 ml of pure (undiluted) solution twice a day (morning and night) after brushing for 30 seconds. It is not informed to the consumer (patient) that the mouthwash should be performed 30 minutes after brushing. Some trademarks advise against brushing immediately after rinsing, using another mouthwash or eating, although without informing about the possible antagonism between chlorhexidine and other dentifrice components.

Trademark	Manufacturer	Composition	Informations about use*
GUM Paroex™	Sunstar Americas, Inc. (Schaumburg, IL, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Peridex™	3M Espe (Minnesota, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Periogard™	Colgate Oral Pharmaceuticals, Inc. (New York, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	Xttrium Lab. (Illinois)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Acclean Chlorhexidine Gluconate 0.12% Oral Rinse	Henry Schein, Inc. (Melville, NY, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Sage Chlorhexidine Gluconate 0.12% Oral Rinse	Sage Products LLC (Cary, IL, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Dash Chlorhexidine Gluconate 0.12% Oral Rinse	Dash Pharmaceuticals LLC (Upper Saddle River, NJ, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	Actavis Mid Atlantic LLC (Baltimore, MD, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	Benco Dental (Pittston, PA, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	Darby Dental Supply, LLC (Jericho, NY, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Pro-den Rx™	Den-mat Holdings, LLC (Lompoc, CA, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	H.J. Harkins Company, Inc. (Grover Beach, CA, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Akorn Chlorhexidine Gluconate	Hi-Tech Pharmacal Co., Inc. (Amityville, NY, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	Lyne Laboratories, Inc. (Brockton, MA, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Patterson Chlorhexidine Gluconate	Patterson Dental Supply Inc. (Saint Paul, MN, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Nupro™	Dentsply Professional (York, PA, USA)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Oris CHX™	Dentsply Professional (York, PA, USA)	Chlorhexidine gluconate 0.12%	Not informed on packaging.
Chlorhexidine Gluconate	Xttrium Laboratories, Inc. (Mount Prospect, IL, US)	Chlorhexidine gluconate 0.12%	Not informed on packaging.

Table 1: *Trademarks available in the US market.*

**Regarding to the orientation to perform the mouthwash 30 minutes after brushing with toothpaste.*

Conclusion

Unfortunately, information regarding the correct mode of use and possible antagonistic reactions between chlorhexidine and other mouthwash or dentifrice substances were not observed. Thus, the dentist must have adequate knowledge when prescribing such antiseptics to ensure successful therapy with chlorhexidine in Dentistry. It is recommended to wait 30 minutes after tooth brushing with dentifrice to start the mouthwash with 0.12% chlorhexidine solution.

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