Use of chlorhexidine varnishes in preventing and treating periodontal disease. A review of the literature

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Abstract
The literature includes numerous clinical trials to assess the effects of chlorhexidine varnishes in patients with chronic gingivitis and periodontitis. The purpose of this study is to review the literature systematically in order to ascertain the clinical effects of the different chlorhexidine varnishes at the periodontal level.
The application of chlorhexidine varnishes seems to have beneficial effects in patients with chronic gingivitis, improving their plaque accumulation and bleeding levels and reducing their gingival index. It is possible to maintain this beneficial effect for prolonged periods of time, although this requires re-applications of the varnish.
This review shows the need for new studies to assess these effects over the long term, in order to establish the number of applications and the interval between them that offer the best results over time.

Key words: *Chlorhexidine varnish, periodontal disease.*

Introduction
Chlorhexidine digluconate is a biguanide that was introduced into the United Kingdom in 1954 as a disinfectant and topical antiseptic. In the 1970s, its ability to inhibit the formation and development of bacterial plaque was demonstrated (1). It is the most effective and safest anti-plaque agent that has been developed to date. Because of its usefulness in controlling bacterial plaque chemically, it is indicated for use in the general population and in high-risk groups of patients (2).
Chlorhexidine is characterised by being a strong base with cationic properties. It mechanism of action is that the cationic molecule binds to the negatively-charged cell walls of the microbes, destabilising their osmotic balance. It acts bacteriostatically when administered at low concentrations, as it encourages the liberation of low molecular weight substances such as phosphorus and potassium. At higher concentrations it acts bactericidally, by causing a precipitation or coagulation of the cytoplasmic content that kills the cells. Its anti-bacterial spectrum covers gram positive and gram negative bacteria (the latter to a lesser extent), fungi and yeasts. It is not a virucide, nor is it effective against acid-alcohol resistant bacilli (3). Its substantivity, the ability of an agent to be retained in particular surroundings, is due to its ability to bind to the carboxyl groups of the mucin that covers the oral mucus and be steadily released from these areas in an active form, displaced by the calcium ions segregated by the salivary glands (4).
The vehicles most often used to administer chlorhexidine are mouthrinses (at concentrations of 0.12% and 0.2%), aerosols (0.12% and 0.2%), gels (0.12% and 1%) and varnishes. The efficacy of chlorhexidine is related to its concentration and the frequency of application (5). The varnishes have been developed over the past decade. They are the most effective form for professional application of

chlorhexidine, as they are easy to apply, do not require collaboration by the patient and although they have an unpleasant flavour, they do not cause discoloration (6).

At the end of the 1980s and beginning of the 1990s, a number of in vitro studies of chlorhexidine liberation were conducted to compare variations in the varnish composition. Schaeken and Haan (7) studied a 50% chlorhexidine varnish containing sodium fluoride at 5%, Schaeken et al. (8) compared 25%, 33% and 40% chlorhexidine varnishes and Balanyk and Sandham (9) studied a varnish with a 10% concentration. The study of Huinziga et al. (10) compared a 1% chlorhexidine varnish, a varnish with 1% thymol and a varnish with both substances. Adding thymol to the chlorhexidine varnish led to a slow liberation of the chlorhexidine, maintaining optimum levels over a three-month period.

Currently, 3 chlorhexidine varnishes are manufactured: Clorzoin®, EC40® and Cervitec®, of which only Cervitec® is available commercially in Spain. The composition and chlorhexidine concentration of each of these varnishes are shown in table 1.

Table 1. Chlorhexidine varnishes available commercially.

Varnish	Composition
EC40 ®	40% Chlorhexidine Sandarac Ethanol
Chlorzoin ®	10% Chlorhexidine Ethanol Polyurethane Methylene chloride Sumatra benzoin
Cervitec ®	1% Chlorhexidine 1% Thymol Ethanol/ethyl acetate Polyvinyl butyral

Adapted from Matthijs and Adriaens (6).

The preventative action of chlorhexidine varnish against periodontal disease was established for the first time in in vitro studies by Petersson et al. (11), who showed the high sensitivity to chlorhexidine of both Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans, bacteria which are strongly associated with the aetiology of periodontal disease. Numerous clinical trials have been conducted to assess the effects of chlorhexidine varnishes in patients with chronic gingivitis and periodontitis. The purpose of this study is to review the literature systematically in order to ascertain the clinical effects of the different chlorhexidine varnishes at the periodontal level.

Materials and Methods

a. *Search strategy*

The literature search was conducted in June 2007 in the PubMed, EMBASE and Cochrane Plus electronic libraries, using the following search terms: "chlorhexidine varnish + periodontal disease", "chlorhexidine varnish + chronic periodontitis", "chlorhexidine varnish + periodontal therapy" y "chlorhexidine varnish + gingivitis". The result was 25 publications in PubMed and 31 in EMBASE. After eliminating those that were repeated, the total number of articles was 36, of which 11 were selected on the basis of their abstracts. After reading the full texts of these articles, 10 clinical trials were selected for review.

b. *Selection criteria*

It was decided to include only controlled clinical trials that assessed the effects of chlorhexidine varnishes clinically in patients with gingivitis or periodontitis. The exclusion criteria were: (a) the use of chlorhexidine in presentations other than varnishes, such as mouthrinses or gel (4 articles); (b) the use of other preventive measures, such as fluoride varnishes, at the same time as the chlorhexidine varnish (5 articles); (c) assessment of the effects of the varnish only at a bacterial or biochemical level, without clinical exploration (3 articles); (d) studies not based on clinical trials, such as in vitro studies or reviews (13 articles); (e) small sample size (1 article).

Results

The 10 studies selected for review are shown in table 2. They were all double-blind randomised controlled trials except for two which were single-blind and two that did not specify the type of blinding employed.

Five of the studies were conducted with the aim of evaluating the effects of different chlorhexidine varnishes in patients with gingivitis through measuring clinical parameters such as plaque indices, bleeding and the Löe and Silness gingival index. Shapira et al. (12) studied the effect of applying a chlorhexidine varnish and an arginine varnish, embedded in a polymer matrix to prolong their liberation, to a group of mentally-retarded patients. The results showed a significant drop in the plaque index at 4 and 8 weeks in the group treated with chlorhexidine; no differences in the gingival index were found. Frentzen et al. (13) observed a reduction in the plaque and bleeding indices after applying a high-concentration chlorhexidine varnish in a group of young adults. As well as measuring the clinical parameters, they grew Streptococcus mutans cultures, where the results showed a reduction in the Streptococcus colonies. Valente et al. (14) and later Bretz et al. (15) studied the effects of a 10% chlorhexidine varnish in adolescents with gingivitis. The results obtained showed a drop in the number of zones scoring 2 and 3 on the Löe and Silness gingival index in the treated group at 3 and 6 months from the initial application. However, the study by

Table 2. Clinical trials conducted with chlorhexidine varnish to assess the clinical effects at the periodontal level.

Authors	Design	Chlor-hexidine varnish	Age of subjects (years)	Number of subjects in treated group	Number of subjects in control group	Number of applications and interval between them	Time from application to assessment	Duration	Results
Cosyn et al. 2007 (18)	DB-RCCT	EC40®	30-75	17 (SRP+EC40)	16 (SRP)	1	1, 3 and 6 months	6 months	pocket ↓ 0'93mm
Cosyn et al. 2006 (19)	DB-RCCT	EC40®	33-75	6 (SRP+EC40)	6 (SRP)	1	1 and 3 months	3 months	pocket ↓ 0.70-1.37
Cosyn et al. 2006 (20)	DB-RCCT	EC40®	32-78	13 (SRP+EC40)	13 (SRP)	1	1, 3, 6 and 9 months	9 months	pocket ↓ 0.62-1.06mm
Clavero et al. 2006 (16)	DB-RCCT	Cervitec®	65-93	27 (Cervitec)	29 (Placebo)	5: 1 week, 1, 3, and 6 months	1, 3 and 6 months from 1st application	6 months	Treated group = control
Cosyn et al. 2005 (21)	SB-RCCT	EC40®	32-78	8 (SRP+EC40)	8 (SRP)	1	1 and 3 months	3 months	pocket ↓ 0.73-1.23mm
Frentzen et al. 2002 (13)	RCCT	EC40®	25-34	20 (EC40)	20 (Placebo)	1	2 and 6 weeks	6 weeks	↓ plaque and bleeding indices
Bretz et al. 2000 (15)	RCCT	Chlorzoin®	10-15	57 (Prophylaxis + Chlorzoin)	53 (Prophyl-axis)	2-4: 1 week, 3 months and 3months +1week	3 and 6 months from start	6 months	↓ gingival index
Dudic et al. 1999 (17)	DB-RCCT	Cervitec®	30-70	20 (Cervitec)	Split mouth (Placebo)	1	2, 4 and 12 weeks	4 months	↓ plaque index
Valente et al. 1996 (14)	SB-RCCT	Chlorzoin®	11-15	57 (Prophylaxis + Chlorzoin)	53 (Prophyl-axis)	1	3 months	3 months	↓ gingival index
Shapira et al. 1994 (12)	DB-RCCT	Chlorhex-idine 1.6%	18-45	11 (Chlorhex-idine1.6%) 11 (Arginine)	12 (Placebo)	Daily for 8 weeks	1, 2, 4 and 8 weeks from start	8 weeks	↓ plaque index

RCCT: random controlled clinical trial
DB: double-blind
SB: single-blind
SRP: scaling and root planing

Clavero et al. (16) found no significant differences between the plaque and bleeding indices of the control group and the group treated with Cervitec®.

The other five studies assessed the effect of chlorhexidine varnishes employed as an adjunct to scaling and root planing in patients with chronic periodontitis. Dudic et al. (17) observed the variations in the presence of plaque and bleeding, the depth of the pockets and the recession in adults with moderate periodontitis, conducted microbiological tests on them and applied Cervitec® following mechanical treatment of the pockets. They only found an increase in plaque in the areas that had been treated with a placebo; the other parameters showed no significant differences compared to the zones treated with the chlorhexidine varnish. Cosyn et al. have conducted several clinical trials (18-21) to study the effect of subgingival application of a high-concentration chlorhexidine varnish following scraping and root planing (SRP). A reduction in pocket depth was found in both the treated group and the control group, to which a placebo varnish had been applied following mechanical treatment of the pockets. The group treated with EC40® achieved an additional reduction that averaged between 0.62 and 0.73 mm. The deepest pockets (≥ 7 mm) were those that obtained the greatest benefit, with reductions that were 0.93 to 1.37 mm greater than in the control group.

Discussion

This systematic review only includes clinical trials published in English that evaluate the periodontal effects of different chlorhexidine varnishes. Comparison of the results obtained in these trials is difficult owing to the considerable variation

in the study parameters, such as varnishes with different chlorhexidine concentrations, the ages of the participants, the number of applications or the clinical indices employed.

Two of the studies included in this review found no significant differences between the control group and the group that had been treated with the varnish. Both of these studies were clinical trials conducted with Cervitec®. Dudic et al. (17) attributed the scant clinical and microbiological effect of the varnish compared to the control group to the good oral hygiene practised by the patients. Clavero et al. (16) concluded that the lack of results was due to various factors such as a lack of oral hygiene or the subjects' wearing removable dentures, which could have affected the salivary levels of certain bacteria.

The rest of the studies found improvements in the clinical parameters following the application of chlorhexidine, obtaining reductions in the plaque and bleeding indices and in the gingival index. Biochemical studies have been conducted that could explain these results. Sköld et al. (22) determined the prostaglandin E2 levels in the crevicular fluid following application of Cervitec® and found a significant reduction in these levels compared to the control group. Subsequently, Yucel-Lindberg et al. (23) observed a reduction in other inflammation mediators such as prostaglandin I2 and leukotriene B4.

Few authors have studied the effect of chlorhexidine varnishes as an adjunct to scraping and root planing. The different studies by Cosyn et al. (18-21) observed reductions in the treated pockets, obtaining the best results in the pockets that were initially the deepest. As well as their clinical observations, Cosyn and Sabzebar (24) studied the microbiological effect of subgingival application of chlorhexidine following SRP and found significant reductions in the levels of Treponema denticola and Tannerella forsythensis.

Conclusions

The application of chlorhexidine varnishes seems to have beneficial effects in patients with chronic gingivitis, improving their plaque accumulation and bleeding levels and reducing their gingival index. It is possible to maintain this beneficial effect for prolonged periods of time, although this requires re-applications of the varnish.

Additionally, subgingival application of high-concentration chlorhexidine varnishes following SRP gives greater reductions in pocket depth than those obtained solely by mechanical treatment of the pockets.

Further studies need to be conducted to assess these effects over the long term, in order to establish the number of applications and the interval between them that offer the best results over time.

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