

## Clinical Impact and Cosmetic Acceptability of Chlorhexidine-enriched Toothpaste and Mouthwash Application on Periodontal Disease: A Randomized Clinical Study

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### ABSTRACT

**Aims:** Oral hygiene is key to prevent periodontal disease (PD). The efficacy of chlorhexidine-containing products has been largely proven, often being tooth discoloration an unwanted associated side-effect. Importantly, some differences related to the pharmaceutical presentation of these products have also been reported. This study aimed to evaluate the efficacy of two different pharmaceutical forms [toothpaste (TP) and mouthwash (MW)] of a new product containing chlorhexidine, dexpantenol, allantoin and bioadhesive excipient (CDAB) (Bexident® Gums Coadjuvant Treatment) on volunteers with PD. Their preferences, acceptability and cosmetic properties, as well as tooth discoloration, were also assessed.

**Materials and methods:** Total 60 subjects showing mild-moderate symptoms of gingivitis were randomly assigned to two different groups: one receiving TP (n = 30) and the other one receiving MW (n = 30). Periodontal disease index (PDI) was used to evaluate clinical signs at baseline (T0) and after 21 days (T21) of daily use of the products. Satisfaction was assessed through the affirmative/negative answers obtained with the visual analog scale (VAS).

**Results:** All participants completed the study. A significant improvement of PDI score after treatment was reported in both groups (T21/T0) ( $p < 0.001$ ). Thus, gingivitis improved from moderate to negative [increase = 20.0% (TP)/36.7% (MW)] and from mild to negative [increase = 56.7% (TP)/50.0% (MW)]. After treatment, all subjects reported to have healthier and/or less bleeding teeth (TP 9.0/9.4; MW 8.0/8.2) and would recommend the product (TP:100%/MW:96.6%) with no specific preference regarding its presentation. No change of teeth color was observed.

**Conclusion:** Subjects with PD who received oral care with a new formulation of either chlorhexidine-containing TP or MW for 21 days, reported a significant improvement of their symptoms and resolution of the gingivitis with no associated tooth discoloration. Patients did not show a specific preference for any of the pharmaceutical presentations.

**Clinical significance:** This new formulation of a chlorhexidine-containing product in both TP and MW forms resulted effective for PD treatment and well accepted by the patients.

**Keywords:** Allantoin, Chlorhexidine, Dexpantenol, Mouthwash, Periodontal-disease-index, Toothpaste.

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The study followed the "Guidelines for the Assessment of Skin Tolerance of Potentially Irritant Cosmetic Ingredients" and the "Guidelines for the Evaluation of the Efficacy of cosmetic Products". All subjects agreed to participate in giving written informed consent.

**Conflict of interest:** Ruiz Magaz V, Ferrer Llovera B and Martí M are external consultants of ISDIN. Garre A is worker of I and D of ISDIN Laboratories.

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### INTRODUCTION

The PD involves the inflammation of the tissues surrounding the teeth (gingivitis and periodontitis) that leads to several degrees of teeth destruction and even tooth loss. Gingivitis and periodontitis are caused by the accumulation of dental plaque around the periodontium. Chronic untreated gingivitis is the initial stage of PD

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and can progress into severe periodontitis, an aggressive disease that causes the destruction of cementum, periodontal ligament, and alveolar bone and therefore, loss of attachment of the teeth.<sup>1,2</sup>

Plaque control is essential in the prevention of PD. Mechanical elimination of bacterial plaque by toothbrushing is an approach to plaque control. However, PD is still a highly prevalent disease.<sup>3</sup> Clinical studies have demonstrated that the incorporation of antimicrobial and functional ingredients into dentifrices and mouthwashes may help control the formation of dental plaque, reducing inflammation and preventing PD progression.<sup>4-6</sup>

Chlorhexidine is a cationic antiseptic that exhibits a wide spectrum of antibacterial activity.<sup>7</sup> Because of its bacteriostatic and bactericidal effects, it has been commonly used as an oral antiplaque rinse in periodontal therapy.<sup>8-10</sup> Interestingly, chlorhexidine also presents an inhibitory effect against some metalloproteases (MMPs), which are involved in inflammation and tissue destruction.<sup>11</sup> However, besides proven efficacy in preventing plaque deposition and gingivitis, chlorhexidine-containing products for dental care have been associated with tooth-surface discoloration as an apparent side effect.<sup>12,13</sup>

An elevated number of chlorhexidine-based preparations for periodontal therapy are available in the market in a variety of formulations including dentifrices (0.4%); mouthwashes in either alcohol-based (ethanol) or non-alcoholic formulations; gels<sup>14</sup> thymol-containing varnishes,<sup>15</sup> chewing gums; and sprays. These preparations may appear in the form of gels, mouthwashes and dentifrices that can be self-applied with or without supervision or administered by a dental healthcare professional.<sup>16</sup> Other functional ingredients that have been incorporated into dental care products include dexpanthenol (an analog of pantothenic acid, known to have anti-inflammatory and re-epithelization/wound-healing effect),<sup>17</sup> and allantoin (that promotes cell proliferation and wound healing).<sup>18</sup> The products chlorhexidine-enriched Bexident<sup>®</sup> Gums Coadjuvant Treatment aimed to combine the antiseptic, anti-inflammatory and regenerative effects of these ingredients against dental bacterial plaque.

The effectiveness of dental care products is based on the selection of active ingredients and the type of formulations. The final concentrations used, retention and release of functional products on oral surfaces and tissues are influenced by the type of formulations selected.<sup>19</sup> Moreover, additional factors such as product acceptance by the patient might have a direct impact on treatment compliance and final product success.<sup>20</sup>

The products tested in the present study are designed to be used for daily dental hygiene in patients suffering

from several degrees of PD. We aimed to evaluate the effectiveness and cosmetic acceptability of two functionally enriched presentations (toothpaste and mouthwash) containing a combination of chlorhexidine, dexpanthenol, allantoin and a bioadhesive excipient (CDAB). We also assessed the discoloration of the tooth surface and patient preferences for the evaluated pharmaceutical forms of the product.

## MATERIALS AND METHODS

### Study Design

A study was performed between April and July of 2016. The protocol used followed the "guidelines for the evaluation of the efficacy of cosmetic products"<sup>21</sup> and the "guidelines for the assessment of skin tolerance of potentially irritant cosmetic ingredients".<sup>22</sup>

### Population

A total of 60 subjects with low to moderate gingivitis according to the periodontal disease index (PDI = 1),<sup>23</sup> and without other oral lesions were included. All gave written informed consent for participation in accordance with the principles of the declaration of Helsinki. Exclusion criteria were intolerance or hypersensitivity to any component of the product, pregnancy, or concomitant disease. Patients receiving treatments that could interfere with the study assessments were also excluded.

All 60 patients underwent a preliminary clinical exam where PDI was evaluated. They were randomly assigned to receive one of the two unlabeled formulations containing a combination of CDAB: toothpaste (TP; n = 30) or mouthwash (MW; n = 30).

### Interventions and Study Outcomes

Products were applied for 21 consecutive days under normal conditions of use. All patients received instructions to brush their teeth for 2 to 3 minutes, twice a day after meals. Participants in the MW group received instructions to additionally use 15 ml of mouthwash product using the provided measuring cup and without dilution, twice a day for 1 to 2 minutes, after the teeth brushing. PDI (clinical signs) and self-assessment on oral cosmetic acceptability (satisfaction) were determined at baseline (T0) and after 21 days (T21) of continuous usage.

Periodontal disease was assessed during the consultation with a dentist using the PDI developed by Ramfjord,<sup>23</sup> that quantifies irreversible destructive disease, as it measures the loss of attachment. PDI ranges from 0 to 6 (periodontal health or gingivitis = 0–3; attachment loss = 4–6) and was used as follows: 0–negative, 1–mild to moderate

inflammatory gingival changes, not extending around the tooth-2, mild to moderately severe gingivitis extending all around the tooth-3, severe gingivitis characterized by marked redness, swelling, tendency to bleed and ulceration; and 4, teeth loss. Product acceptability was assessed by the volunteers who were asked to complete a questionnaire after 21 days using the product.

### Statistical Analysis

Data are expressed as the percentage of patients falling in each category of the PDI scale. Chi-squared test was used for comparative analysis between study groups at baseline and at 21 days after starting treatments. Statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., IL, USA) and Graph Pad Prism 7.0 for visualization (GraphPad Software Inc, CA, USA).

### RESULTS

All participants (n = 60) completed the study with no dropouts. Demographic data is given in Table 1.

Both groups achieved a significant improvement of PDI score after 21 days using chlorhexidine-enriched

formulations. The percentage of patients showing no gingivitis (negative) significantly increased in both TP and MW groups (Chi-squared test, p < 0.001) (Fig. 1). An improvement of gingivitis from moderate to negative [increase = 20.0% (TP)/36.7% (MW)] and from mild to negative [increase = 56.7% (TP)/50.0% (MW)] was observed. None of the patients presented teeth loss.

Results from cosmetic acceptability analysis (Fig. 2) showed that both CBAD-containing products (TP and MW) were appreciated by all participants. The number of patients indicating a reduction in bleeding when brushing and gum inflammation was above 90.0% for both TP and MW (A). No change on teeth color was observed (TP 90.0%/ MW 96.7%). After 21 days of use, patients indicated that they would be willing to recommend the received products by 100% (TP) and 96.6% (MW). From 0 to 10, final mean scores given by participants were 8.1 and 7.1, for TP and MW respectively (Fig. 2). Subjects reported to have healthier and/or less bleeding teeth (TP 9.0/9.4; MW 8.0/8.2) No significant differences were observed when comparing both products. The products were well tolerated.

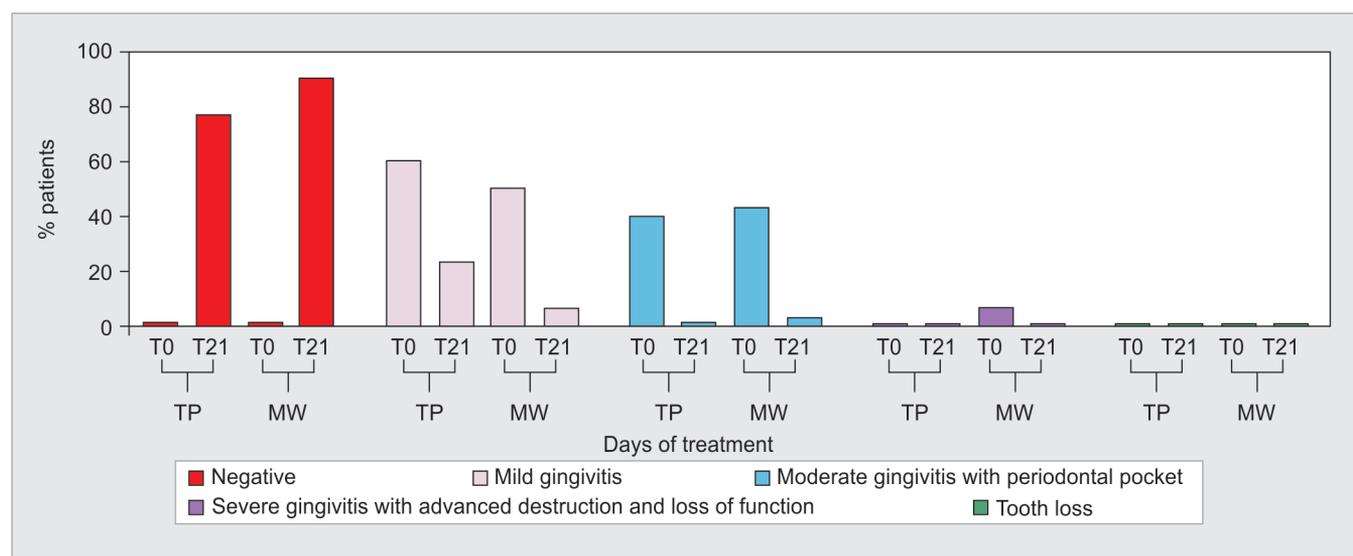
### DISCUSSION

Several chlorhexidine-based preparations are available in the market, including toothpaste and mouthwash formulations. However, their effectiveness in periodontal disease management may vary greatly because of the formulation that has a relevant impact on the retention and release of active ingredients.<sup>19,20</sup> Thus, some ingredients such as detergents, dentifrice abrasives, calcium ions, and sodium monofluorophosphate may compromise the antimicrobial and antiplaque properties of chlorhexidine.<sup>19</sup>

**Table 1:** Demographic data of the study groups

	Toothpaste (TP)	Mouthwash (MW)
n	30	30
Female (%)	50%	60%
Age, mean (min-max)	41.3 (18-70)	41.2 (18-70)
Smoking (%)	26.7%	30.0%
Coffee (%)	86.7%	83.3%
Alcohol (sporadic use) (%)	66.7%	7.0%
Allergies (pollen) (%)	6.7%	6.7%

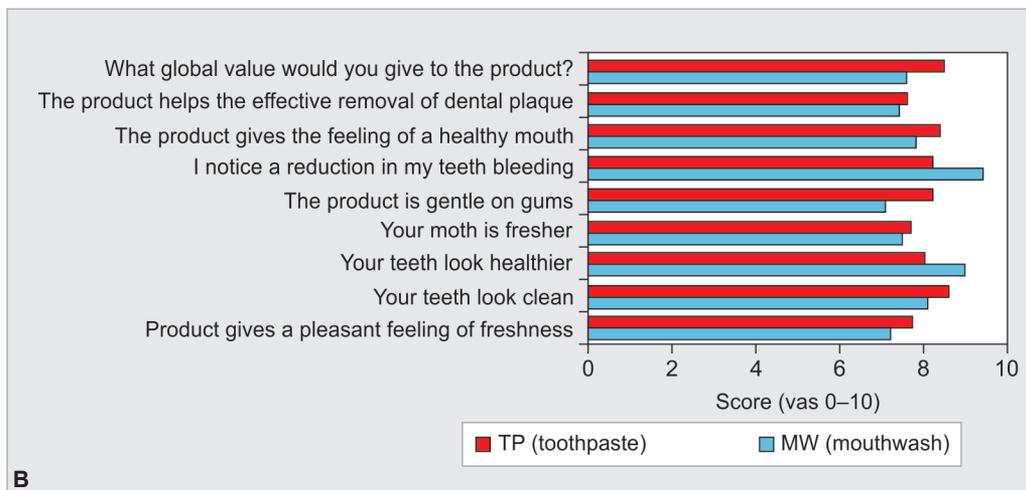
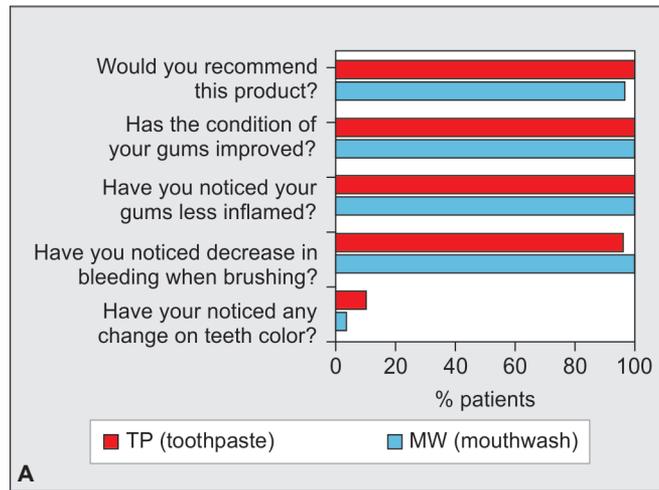
Abbreviations: TP = Toothpaste, MW = Mouthwash.



**Notes:** Periodontal disease index. Longitudinal evolution comparing baseline (T0) and after 3 weeks of treatment (T21)

**Abbreviations:** Toothpaste (TP); Mouthwash (MW)

**Fig. 1:** Periodontal disease index (PDI) after 21 days of treatment with toothpaste (TP) and mouthwash (MW)



Abbreviation: Visual analog scale (VAS)

**Figs 2A and B:** Cosmetic acceptability (A) self-efficacy perception at day 21; (B) global evaluation and cosmeticity perception after 21 days of treatment with toothpaste (TP) and mouthwash (MW)

Chlorhexidine-enriched products have shown efficacy in reducing plaque formation and also gingivitis.<sup>12,14,24,25</sup> However, despite encouraging results have been obtained with chlorhexidine-containing dentifrices,<sup>26,27</sup> it is apparent that the activity of MW is difficult to equal.<sup>28</sup> In 2015 Supranoto et al. published a systematic review,<sup>19</sup> in which the available scientific evidence on the effectiveness of both types chlorhexidine-containing formulations (TP and MW) on a plaque, bleeding, gingival inflammation and tooth discoloration scores were evaluated. Five randomized controlled trials were included, in which a positive effect of MW over TP on plaque scores was observed in three of them.

Furthermore, no significant differences were found in relation to gingival index and bleeding scores, while chlorhexidine MW showed significantly more tooth discoloration than the TP. The authors concluded that TP was significantly less effective in plaque inhibition compared to MW when used in a non-brushing model. Therefore, MW was the first one of choice when daily oral hygiene cannot be performed. However, the study also demonstrated that, as a corollary, significantly more tooth discoloration was observed with the MW.

In the present study, both products (TP and MW) reduced the PD index after 21 days of continuous use, and patients scored positively their action on bleeding and gum inflammation. Importantly, despite the widely reported brown staining of the teeth as a chlorhexidine-associated side effect, our results demonstrated that these particular formulations did not have a tooth discoloration effect. This might explain why participants did not show a preference for a specific pharmaceutical form and reported good cosmetic acceptability for both.

Cosmetic acceptability is one of the main factors affecting adherence to the different product formulations, with the subsequent direct effect on the final exposure to the functional product.<sup>20</sup> The results from the present study showed that both products were very well appreciated by all study participants. Besides the fact that mouthwash represents an additional product to be used, self-reported questionnaires showed good results in cosmetic acceptability in MW group, indicating that they would continue and recommend the use of the product received after the study.

One limitation of this study lies in the fact that the outcomes were evaluated at short-term and, consequently, further research is needed to infer the long-term efficacy of both products. However, our studies show promising effects of both TP and MW after 21 days of usage, a time which is in line with what it has been reported in some recent studies evaluating chlorhexidine-containing products.<sup>29,30</sup> On the other hand, another possible limitation could be related to the methodology used to assess periodontal disease. Thus, some complementary scores and/or manual probes could have been applied. Nevertheless, all indices to evaluate periodontal disease show advantages and disadvantages<sup>31</sup> and the PDI<sup>23</sup> remains a useful method widely used in clinical studies.<sup>29,32-34</sup>

In summary, our results support the incorporation of both pharmaceutical presentations of these product formulations into daily routine dental care as an effective method to manage PD.

## CONCLUSION

The present study evaluated the effectiveness of two functionally enriched presentations containing chlorhexidine (TP and MW) on PD (Bexident® Gums Coadjuvant Treatment), cosmetic acceptability, patient's preference, and tooth discoloration. Results showed very good effectiveness after product application during 21 consecutive days with all patients showing good acceptability for both pharmaceutical forms. No preference for any of the presentations was reported. Importantly, discoloration was not observed with any of the tested products. Our results suggest that these two formulations may be of use in patients with mild-to-moderate gingivitis to improve the symptoms and oral health and pave the way for future studies to assess these products with larger cohorts of patients.

## CLINICAL SIGNIFICANCE

Enriched formulations containing CDAB in both TP and MW presentations were effective in reducing plaque and the gingival inflammation with no tooth discoloration-associated effect.

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