The efficacy of 0.12% chlorhexidine versus 0.12% chlorhexidine plus hyaluronic acid mouthwash on healing of submerged single implant insertion areas: a short-term randomized controlled clinical trial

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Abstract

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Reference


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The efficacy of 0.12% chlorhexidine versus 0.12% chlorhexidine plus hyaluronic acid mouthwash on healing of submerged single implant insertion areas: a short-term randomized controlled clinical trial

Abstract: Objectives: The study was performed to evaluate the incidence of post-surgical adverse events at submerged implant sites as well as the antiplaque, antigingivitis and antistaining effects in the entire dentition of patients treated with two mouthwashes. Methods: The present randomized controlled clinical study considered 40 patients subjected to dental implant treatment. Two 0.12% chlorhexidine mouthwashes were compared for 15 days: one with 0.1% hyaluronic acid (CHX⊗HYL group) and one without it (CHX group). Surgical outcome variables, and plaque, gingival, and staining indexes were recorded. Results: Significant differences were found between the two rinses regarding the presence of oedema within 2 days after surgery (20% for the CHX⊗HYL group and 78% for the CHX group). No other significant differences were recorded between the two mouthwashes. No intergroup differences in plaque, staining and gingivitis indexes were registered. The intragroup analysis revealed that for the plaque and gingival indexes, the differences between the baseline values (before surgery) and those at 15 days were all found to be significant just for CHX⊗HYL rinse, with final values ranging from 0.18 to 0.23 for the plaque index and from 0.06 to 0.07 for the gingival index. The staining index increased for both mouthwash types with significant results (with final value of 0.19 and 0.31 for CHX⊗HYL and CHX groups, respectively). Conclusions: In the sites of patients subjected to dental implant placement, an additional anti-oedematigenous effect in early healing seemed to be disclosed for 0.12% CHX⊗HYL mouthwash. Regarding antiplaque and antigingivitis activities, HYL seemed to be ineffective.

Key words: Chlorhexidine; dental staining; hyaluronic acid; mouthwashes; submerged single implant

Introduction

After an oral surgical procedure, maintaining a high level of oral hygiene is a very important factor for the success of any dental implant insertion technique (1).

Several topical antimicrobial substances used as an adjunct to mechanical cleaning procedures, such as essential oils, metal salts, oxygenating...
agents and others, generally have been employed in plaque control (2–5). A recent review paper suggested that profession-
ally and patient-administered mechanical plaque control alone should be considered the standard of care in the management of peri-implant mucositis (6). However, the gold standard of antiplaque agents has been chlorhexidine (CHX, a dicationic chlorophenyl biguanide), its broad antimicrobial spectrum is being verified by several studies in the literature testing effi-
cacy (5), and it has been used as a positive control in many clinical trials for several mouthrinses. CHX showed substantivity (i.e. its binding) in the oral cavity, to both hard and soft tis-
sues, producing a very durable effect, including long after (7–12 h) the moment of its application (7–11). A very recent sys-
tematic review suggested a CHX optimal dose of 20 mg twice daily, regardless of the concentration used (11). A mouthwash volume of 15 ml CHX 0.12% provided a similar dose (18 mg) to that of 10 ml CHX 0.20% (20 mg), so that a concentration of 0.12% CHX seemed to appear to be as effective as the one of 0.2% (12). Another systematic review concluded that there is a small but statistically significant difference in the effect on plaque between a 0.12% and a 0.2% CHX rinse, whereas no difference in reducing gingivitis between the two concentra-
tions could be established (10).

The linear polymer of glucuronic acid N-acetylglucosamine disaccharide (hyaluronic acid, HYL) seems to be involved both in the reduction in inflammatory responses, due to its anti-
oedematigenous and bacteriostatic effects (13, 14), and in the promotion of a re-epithelization phenomenon (15). Hyaluronic acid has also been employed in the treatment of patients with gingivitis after supragingival scaling (16).

The primary aim of the present paper was to compare, over a two-week period, the efficacy of the two types of mouth-
wash, both being a 0.12% chlorhexidine mouthwash, one with hyaluronic acid (CHX@HYL) and the other without hyaluronic acid (CHX), through an analysis of the results of the clinical outcome parameters, which were oedema, inflammation around the suture area and granulation tissue in areas where sub-
merged dental implants were placed; patient compliance was also followed up.

The secondary aim was to assess the effectiveness on pla-
que, bleeding, and staining index reduction in the two mouth-
rinses (CHX@HYL versus CHX); a correlation analysis was also performed between the consumption of coloured bever-
ages and staining index.

Study population and methodology

Study design/sample

Forty subjects were enrolled from January 2010 to September 2011 and were referred to the Dental Clinic of the Tuscan Stomatologic Institute, Viareggio, Italy. Before enrolment, each patient received an explanation of the objectives of the study, and written informed consent was requested. Approval for the conduct of the trial was obtained from the ethical committee of the Institutional Review Board (146/2012).

For the present double-masked parallel-arm randomized controlled clinical trial, regarding the enrolment of patients, all of whom had undergone a dental implant insertion for fixed prosthetic rehabilitation, the following criteria were employed:

Inclusion criteria:

At least 18 years of age.

Patients requiring dental implant insertion in a single-tooth edentulous area with the presence of healthy teeth adjacent to the healed extracted site (tooth without fixed prosthetic restoration, without failed dental restorative materials or restored cervical abrasion, abfraction, resorption lesion).

A maximum of two dental implant placements per patient.

If two implants were placed (with an adjunctive implant positioned in a different side or arch), just one site, following all inclusion criteria, was considered.

Exclusion criteria:

General contraindication to dental implant treatment (uncontrolled diabetes and severe cardiovascular or infec-
tious diseases).

Intravenous and oral bisphosphonate therapy.

Presence of severe, moderate or mild untreated periodontal disease.

Unwillingness to return for the follow-up examination.

Use of more than 10 cigarettes per day (risk factor for dental implant failure). (17)

Two types of mouthwash were applied and were labelled with an X (CHX, 0.12% chlorhexidine, 15 ml Dentosan®) or a Y (CHX@HYL, 0.12% chlorhexidine mouthwash plus 0.1% hyaluronic acid, 9 ml Dentosan® chlorhexidine 0.2% plus 6 ml Aftamed® 25 mg/100 g²).

Before surgery, a dental assistant (DC), not involved in the selection or treatment of the patients, assigned each subject to one of the two groups using an exactly symmetric binomial random binary sequence (X or Y), generated previous to patient selection;4 patients, after scaling, were trained in modified Bass brushing technique, using a manual toothbrush and a toothpaste having no influence on CHX effects, as well as in the use of dental floss (18).

The collection of data and the acquisition of clinical indexes were carried out under the same conditions by a single blinded researcher (MR), who was unaware of the mouthrinse used by the participants; the examiner was trained during a calibration meeting in which repeated measures were acquired on a test group of patients and the correlation coefficient tests, in order to evaluate the intra-examiner calibration, showed significant results in the range from 0.90 to 0.98. Following the surgical procedure, each patient rinsed their whole oral cavity with

1 Dentosan® chlorhexidine 0.12% Cilag International GmbH, Johnson & John-
son Family of Consumer Companies.

2 Dentosan® chlorhexidine 0.2% Cilag International GmbH, Johnson & John-
son Family of Consumer Companies.

3 Aftamed® 25 mg/100 g: Cilag International GmbH, Johnson & Johnson Family of Consumer Companies.

4 Statistics Toolbox, MatLab 7.0.1, The MathWorks, Natick, MA.
mouthwash twice a day (in the morning and in the evening) for 15 days, and which was then expectorated. All participants were instructed to refrain from using water mouthrinse for one hour, and compliance was checked gathering a rinsing calendar directly self-recorded by the patients.

For the present surgical treatment, CHX was used on a short-term basis, to reduce negative clinical outcomes for the surgical site, in which conventional plaque control is difficult (11).

Surgical treatment

Patients received prophylactic antibiotic therapy (2 g amoxicillin or, if allergic to penicillin, 600 mg clindamycin) 1 h before dental implant placement. Patients were treated under local anaesthesia using lidocaine with adrenaline 1:50 000. After mid-crestal incision, full thickness mucoperiosteal flap was minimally elevated and osteotomy for each site was prepared according to the procedures recommended by the manufacturer. The initial guide drill was used to perforate the cortex, followed by the use of the 2-mm twist drill in accordance with the position and angulation planned by the implant surgical guide. The osteotomy was, subsequently, widened according to the manufacturer’s indication. A final countersink was used to prepare the 2-mm coronal part of the ridge to the same diameter of the implant. Subsequently, the implants were inserted by means of surgical unit5 with a calibrated maximum torque of 40 Ncm at predetermined 30 rpm. All titanium dental implants, root form, internal hex, rough-surfaced screws6, were inserted with the implant platform at the bone crest level. Cover screws were placed and flaps were closed over the implant with simple interrupted suture7. All patients were instructed to continue with prophylactic antibiotic therapy (1 g amoxicillin or 300 mg clindamycin) two times a day for 4 days, and naproxen sodium 550 mg tablets were prescribed as an anti-inflammatory to be taken twice for the first day, only if it was required.

Around the site of dental implant placement, toothbrushing was not allowed, and mouthwashing was the only choice. The implants used for this study were all of the same brand and type6. The submerged implants included in this study were restored 3–4 months after implant placement. All surgical procedures were performed by a single surgeon (UC).

Variables and data collection

All patients were subjected to an oral hygiene session prior to the surgery in order to provide a more favourable oral environment for wound healing: all stain, calculus and plaque were removed. All the participants in the study remained blinded until the end of the study.

Demographic data

Data were collected for each patient: age, gender and location for dental implant placement. Regarding habits related to the consumption of wine, tea and coffee, the number of times per day was recorded during the observation period.

Primary predictor variables

The presence of hyaluronic acid in the chlorhexidine mouthwash, for the CHX⊗HYL group, and the absence of hyaluronic acid in the chlorhexidine mouthwash, for the CHX group, were the primary predictor variables.

Primary outcome variables

Three hours after surgery, at 2 and at 15 days, oedema, inflammation around the suture area and granulation tissue were recorded as binary events (presence versus absence) using the following scale: 0 = absence and 1 = presence as per Cortellini (19) to correctly analyse the healing of the site after dental implant placement.

Secondary outcome variables

At baseline (before surgery), and at 2 and 15 days after surgery, a comprehensive mouth plaque, bleeding and staining index was computed by means of the three standard indexes acquired.

Plaque index (PI): plaque was revealed by plaque-disclosing tablets8 (two per patient). Six surfaces were examined per tooth (disto-buccal, mid-buccal, mesio-buccal, disto-lingual, mid-lingual and mesio-lingual). The absence or presence of plaque was recorded for each surface, as per Grundemann (20).

Bleeding index on marginal probing (BIMP): bleeding on marginal probing was examined for six surfaces per tooth (disto-buccal, mid-buccal, mesio-buccal, disto-lingual, mid-lingual and mesio-lingual); the presence of bleeding was tested for within 1 min after probing the gingival margin at an angle of approximately 60° to the longitudinal axis of the tooth, on a scale from 0 to 2 (0 = non-bleeding; 1 = pinprick bleeding; 2 = excessive bleeding), as per Grundemann (20).

Staining index (SI): four areas were examined per tooth as per Grundemann (20), one incisal, one gingival and two approximals. Intensity of staining was scored as per Lobene (0 = no stain; 1 = light stain; 2 = moderate stain; 3 = heavy stain) (21, 22).

Moreover, any side effects arising during mouthwash treatment, such as a lesion in the oral mucosa or taste modification, encountered by patients were also documented.
Statistical analysis

Power analysis was employed to determine the sample size of the CHX⊗HYL group versus the CHX group, using a 0.05 significance level and a power of 80%, based on the values regarding proportions, mean and standard deviations reported in previous studies concerning the changes in surgical outcome variables, and the indexes above described (19, 23). Minimum sample size estimate was generated comparing the proportions related to the variable ‘inflammation around suture’ (0.4782 and 0.625) at 1 week (19). Even if a sample of 42 patients sufficed the statistical analysis, a sample increment of 25% in the enrolment step was searched due to a potential patient drop-out.

Spearman’s rank correlation test was applied to evaluate the intra-examiner calibration. Differences between the CHX⊗HYL and the CHX groups, in terms of all surgical outcome variables, were tested at 3 h, at 2 days and at 15 days after surgery, using Fisher’s exact test.

Full-mouth indexes obtained from the ranked single-tooth parameters were used as secondary response variables. Normal distribution for each variable was not confirmed by the Shapiro–Wilk test. For all three of the indexes PI, BIMP and SI, pair comparisons between the CHX⊗HYL and CHX groups were performed by the Wilcoxon two-sided rank-sum test for independent samples, whereas differences between times were searched for using the Wilcoxon two-sided signed-rank test.

For the final time point (15 days), pairwise linear correlations between the variables related to each patient’s beverage consumption and the three indexes were performed employing the Spearman’s rank correlation test. All measurements in the tables are described as mean and standard deviations: mean ± SD. The statistical significance was set at \( P = 0.05 \). Power analysis and effect of the sample size were determined (0.05 significance level with power of 90%). All statistical analyses were performed by a matrix laboratory\(^4,9\).

Results

In this study, a total of 40 patients were enrolled (24 men and 16 women, aged 54.7 ± 12.1 years). Table 1 summarizes the demographic data from the two groups. All patients certified in their rinsing calendars that they meticulously followed indications of the present paper, giving a 100% of compliance. No patient dropout occurred.

Neither allergic reactions to CHX and/or HYL or antibiotics nor major complications were recorded in the subjects, all of whom had been treated by dental implant placement. Two patients (belonging to CHX group) of the 40 continued analgesic therapy till the third day. Abovementioned two patients were excluded from statistical analysis due to prospective cumulative effects on surgical outcomes of the analgesic/anti-inflammatory drug; however, these patients showed inflammation around sutures and oedema both at baseline and at 2 days after surgery. During the mouthwash treatment, no minor side effects, such as burning mouth or taste modification, were reported by any of the patients.

Among the primary surgical outcome variables (oedema, inflammation around the suture area and granulation tissue), the incidence of oedema showed significant differences between the two groups within 2 days after surgery (with 9 and 15 events at the 3-h control, respectively, for the CHX⊗HYL and CHX groups, with a \( P \)-value of 0.0205; and with 4 and 15 events at the 2-day control, respectively, for the CHX⊗HYL and CHX groups, with a \( P \)-value of 0.0009). Significant differences between the two groups were displayed neither for variables related to inflammation around the suture area nor for that related to the granulation tissue (Table 2). Table 2 also shows the estimated size of the effect for all outcome variables presented. In Table 2 are also showed the descriptions and statistics of the three indexes (PI, BIMP and SI). Neither for all indexes nor for the percentages of colonized sites, significant differences were found between the two mouthwashes at any of the time points of the survey, whereas a similarity between indexes and percentage of colonized sites can be revealed when intragroup significances were investigated.

As regards the plaque index, in the CHX⊗HYL and CHX groups, all differences were significant (with \( P \) from 0.0029 to 0.0001), except for the comparison between 2- and 15-day time in both CHX⊗HYL and CHX groups. Regarding the BIMPs, the pre-operative values (0.14 ± 0.10 and 0.13 ± 0.11 for the CHX⊗HYL and CHX groups, respectively) were different from those at the 2-day (0.09 ± 0.08 and 0.09 ± 0.09 for rinses in the CHX⊗HYL and CHX groups, respectively) and 15-day time point (0.07 ± 0.04) just for the CHX⊗HYL mouthwash type, all with significant \( P \)-values less than 0.008. In Table 2 is presented the distribution of the staining index, which seemed to increase for both mouthwash types, from 0.14 ± 0.17 to 0.19 ± 0.14 in the CHX⊗HYL group, and from 0.12 ± 0.19 to 0.31 ± 0.34 in the CHX group, but with no significance.

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\(^{1}\)Database Toolbox, MarLab 7.0.1, The MathWorks, Natick, MA.
Table 2. Results regarding surgical outcome variables (oedema, inflammation around the suture area and granulation tissue) and regarding secondary outcome variables (plaque index, bleeding index on marginal probing and staining index) recorded at 3 h after surgery and then at 2 and 15 days

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Significance and power between groups</th>
<th>Follow-up times</th>
<th>Comparisons between times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 h</td>
<td>2 days</td>
</tr>
<tr>
<td>Inflammation around suture area (Y/N)</td>
<td>CHX@HYL</td>
<td></td>
<td>5/15 (25%)</td>
<td>8/10 (44%)</td>
</tr>
<tr>
<td></td>
<td>CHX</td>
<td></td>
<td>8/10 (44%)</td>
<td>8/10 (44%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>P-value CHX versus CHX@HYL</td>
<td>0.3071†</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Post hoc estimated effect size</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post hoc power analysis</td>
<td>0.7812</td>
</tr>
<tr>
<td>Oedema (Y/N)</td>
<td>CHX@HYL</td>
<td></td>
<td>9/11 (45%)</td>
<td>15/3 (83%)</td>
</tr>
<tr>
<td></td>
<td>CHX</td>
<td></td>
<td>4/16 (20%)</td>
<td>14/4 (78%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>P-value CHX versus CHX@HYL</td>
<td>0.0205†</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Post hoc estimated effect size</td>
<td>15</td>
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<td></td>
<td></td>
<td></td>
<td>Post hoc power analysis</td>
<td>0.9998</td>
</tr>
<tr>
<td>Granulation tissue (Y/N)</td>
<td>CHX@HYL</td>
<td></td>
<td>0/20 (0%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td></td>
<td>CHX</td>
<td></td>
<td>0/18 (0%)</td>
<td>1/17 (6%)</td>
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<td></td>
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<td></td>
<td>P-value CHX versus CHX@HYL</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
<td>Post hoc estimated effect size</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
<td>Post hoc power analysis</td>
<td>–</td>
</tr>
<tr>
<td>Plaque index (PI)</td>
<td>CHX@HYL</td>
<td></td>
<td>0.45 ± 0.15</td>
<td>0.34 ± 0.17</td>
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<td></td>
<td>CHX</td>
<td></td>
<td>0.34 ± 0.17</td>
<td>0.32 ± 0.23</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>P-value CHX versus CHX@HYL</td>
<td>0.0582*</td>
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<td></td>
<td>Post hoc estimated effect size</td>
<td>26</td>
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<td></td>
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<td>Post hoc power analysis</td>
<td>0.9803</td>
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<tr>
<td>Bleeding index on marginal probing (BIMP)</td>
<td>CHX@HYL</td>
<td></td>
<td>0.14 ± 0.10</td>
<td>0.13 ± 0.11</td>
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<td></td>
<td>CHX</td>
<td></td>
<td>0.09 ± 0.08</td>
<td>0.09 ± 0.09</td>
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<td></td>
<td>P-value CHX versus CHX@HYL</td>
<td>0.6393*</td>
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<td>Post hoc estimated effect size</td>
<td>1622</td>
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<td></td>
<td></td>
<td></td>
<td>Post hoc power analysis</td>
<td>0.0773</td>
</tr>
<tr>
<td>Staining index (SI)</td>
<td>CHX@HYL</td>
<td></td>
<td>0.14 ± 0.17</td>
<td>0.12 ± 0.19</td>
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<td></td>
<td>CHX</td>
<td></td>
<td>0.18 ± 0.29</td>
<td>0.18 ± 0.29</td>
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<td></td>
<td></td>
<td></td>
<td>P-value CHX versus CHX@HYL</td>
<td>0.7844*</td>
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<td></td>
<td></td>
<td></td>
<td>Post hoc estimated effect size</td>
<td>1375</td>
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<td></td>
<td></td>
<td>Post hoc power analysis</td>
<td>0.0827</td>
</tr>
</tbody>
</table>

Significance (P-value) for differences between CHX@HYL versus CHX and between times tested by Wilcoxon’s tests (*) and Fisher’s exact test (†). P values indicating statistically significant difference are shown in bold. Post hoc estimated effects on sample size (P = 0.05 with 0.90 power) and post hoc power analysis were also calculated. Two patients belonging to CHX group under naproxen sodium 550 mg tablets were excluded from analysis.
No significant correlations were found between the staining index and the consumption of any of the coloured beverages for either type of rinse.

Discussion

Short-term effects of chlorhexidine mouthwash plus hyaluronic acid have been investigated in patients underwent to delayed dental implant placement. Although hyaluronic acid seemed to show anti-inflammatory and anti-oedematigenous effects (24), its use as antibacterial mouthwash (25) and in the treatment of peri-implant pathologies (23) appeared questionable. The positive effect on clinical healing of the wound (26) and on symptoms’ management of the recurrent aphthous ulceration (27) was verified.

In the present study, anti-oedematigenous effect seemed to be confirmed; in fact, in patients subjected to submerged dental implant placements and treated with CHX mouthwash plus HYL, the incidence of oedema within 2 days post-surgery was significantly lower than that seen in patients treated with CHX rinse alone. Oedema was recorded at the second day in 20% of patients belonging to the CHX/HYL group and in 78% of patients belonging to the CHX group: the post hoc estimated size about oedema events (7) presented in Table 2 seemed to confirm the effectiveness of the CHX/HYL mouthrinse at 2-day follow-up. After periodontal flap surgery, Cortellini prescribed to patients a 10 ml of 0.2% CHX rinse two times per day. He recorded, at 1 week, oedema and inflammation around the suture area, respectively, in 42% and in 62% of the patients (19), confirming the present surgical outcomes regarding the 0.12% CHX group. The absence of other minor clinical side effects verified results coming from previous authors (28, 29).

Due to the persistent bacteriostatic action lasting in excess of 12 h, CHX mouthrinses with different formulations (0.12% and 0.2%) are nowadays the ‘gold standard’ against local side effects of delayed wound healing in the presence of commonly used antiseptics, attested that H2O2 potentially retards the contribution of fibroblasts to the healing process, whereas CHX had fewer detrimental effects on fibroblast activity.

According to the American Dental Association, a clinical study concerning ‘adjunctive’ devices for controlling plaque and gingivitis demanded an evaluation period of at least 4 weeks (11). Even if this very short-term study could not yield conclusive results regarding the overall modifications of indexes between the two mouthwashes employed, however, the very quick decrease in the plaque and bleeding indexes could be a positive factor for surgical short-term outcome after dental implant placement.

Moreover, the clinical significance of the present study is affected by some limitations: the short term of the study, at 15-day follow-up two patients belonging to CHX group showed oedema in the surgical site and no additional information were acquired; and the small sample size, the inflammation around sutures at 2 days of survey was twofold for the CHX (44%) respect to CHX/HYL group (20%) but without statistical significance. Another limitation for the evaluation of early effectiveness of the CHX/HYL mouthrinse for submerged dental implant placement was the employment of an antibiotic during the first post-operative follow-up (at 2 days); however, the administration of the same antibiotic to all patients led to similar cumulative effects for the two mouthrinses. Therefore, further investigation, with an increased number
of subjects and an expanded follow-up, is necessary to confirm these current findings.

Conclusions
In the healing site of patients subjected to dental implant placements, no difference between groups was observed at 15 days post-surgery; however, an anti-oedematogenous additional effect in early healing seemed to be disclosed for 0.12% CHX®HYL mouthwash. No significant differences in antiplaque, antigingivitis and antistaining effects were revealed by the comparison between the two rinses; however, when either 0.12% CHX®HYL or 0.12% CHX mouthwash was employed, significant reductions in plaque and bleeding were observed; moreover, both the rinses seemed to be exhibited a tooth-staining effect.

Clinical Relevance

Scientific rationale for the study
In the surgical procedure of dental implants’ placement, chlorhexidine rinse was generally applied until suture removal in order to reduce the risk of infection and to aid healing. Therapeutic responses of adjunctive compounds (such as hyaluronan) on wound healing, on the health of the surgical site and on neighbouring teeth could be proven.

Principal findings
Differences between the chlorhexidine mouthwashes (with or without hyaluronan) were revealed when analysing the primary outcome variables linked to dental implant treatment (inflammation around suture area and oedema), suggesting different effects for the two rinses.

Practical implications
Significant results were obtained for the chlorhexidine mouthwash plus hyaluronan, yielding anti-oedematogenous additional effects on surgically treated sites.

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Conflict of interest
All of the authors declare that there exists no conflict of interest, nor financial relationships between any author and any of the products involved in this study. All the materials were commercial products, and no financial support or discount was given by the manufacturers.

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