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Research article

The clinical effect of sodium hypochlorite oral rinse on peri-implantitis lesion: A pilot study

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ABSTRACT

Peri-implantitis poses an imminent challenge to the field of implant dentistry. Considering the promising findings of sodium hypochlorite and periodontal lesions, the aim of the present study was to evaluate the clinical effects of sodium hypochlorite oral rinse on peri-implantitis lesions. Twelve peri-implantitis patients were instructed to rinse with 15 mL of a fresh solution of 0.25% sodium hypochlorite for 30 s twice a week for 3 months. At baseline and 3-month visits, probing depth and modified sulcular bleeding index were recorded at 6 points per lesion (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual). Individual and total bacterial loads of 18 pre-designated species of microorganisms were analyzed by real-time PCR methods. Probing depth decreased after the experiment, with an average difference of 1.1 mm and a standard deviation of 1.7 mm. The modified sulcular bleeding index decreased by a mean value of 0.8 with a standard deviation of 1.1. This study demonstrated the clinical effects of sodium hypochlorite oral rinse on peri-implantitis lesions and the reduction of periodontal probing depth and gingival bleeding index. This study suggested that the concentration of 0.25% be used for treatment of peri-implantitis.

1. Introduction

Peri-implantitis is of great concern and poses an imminent challenge to the field of implant dentistry [1–5]. It was reported in 2010 that peri-implantitis exists in close to half of implant patients [6]. In 2016, a retrospective study from Derks et al. indicated a 45% prevalence among implant patients in Sweden [7]. Against the increasing prevalence of peri-implantitis, conventional treatments have been classified as either surgical or non-surgical methods [8]. Non-surgical methods comprise mechanical debridement, local or systemic antibiotics, irrigation with antiseptics, and laser therapy [9]. The clinical outcomes of non-surgical therapy alone are not consistent [10]. The Committee of the 6th European Workshop on Periodontology, which dealt with the efficacy of peri-implantitis treatments in a randomized controlled human study, concluded that non-surgical therapy alone was not effective against peri-implantitis lesions [11]. None of the non-surgical methods, alone or combined, were comparable to the treatment outcomes of surgical methods [12]. A 58% resolution of peri-implantitis lesions was reported after surgical intervention during 5-year follow-up period from nine partially dentate individual with 44 implants [13]. Recent meta-analysis revealed bleeding reduction ranging

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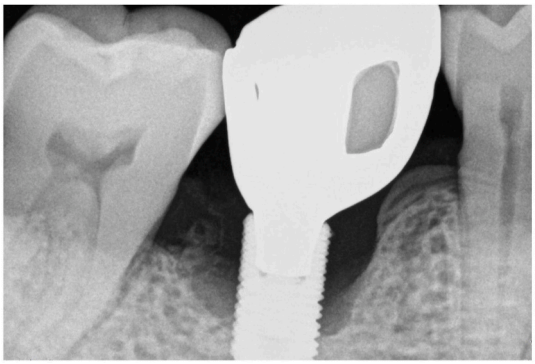

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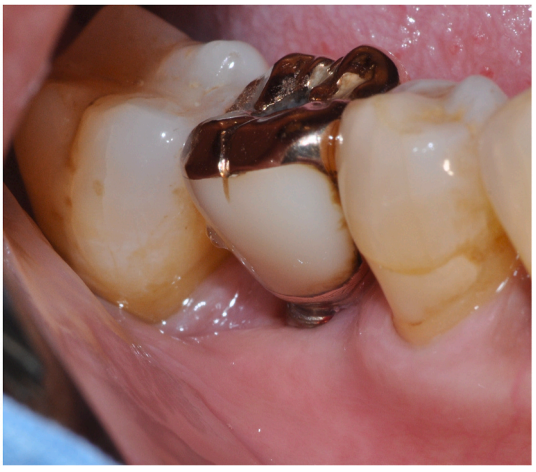

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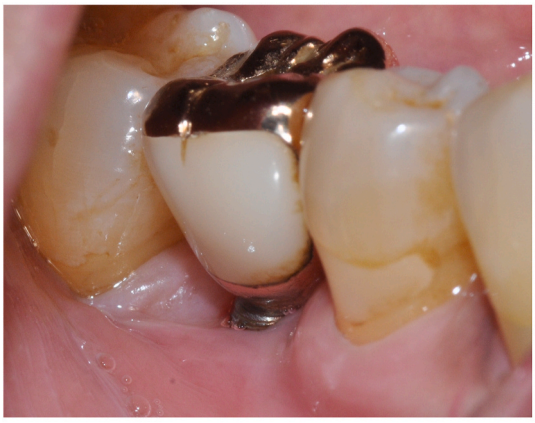

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Fig. 1. Clinical and radiographical evaluation A. Preoperative radiograph B. Buccal view at baseline evaluation C. Clinical photograph at follow-up evaluation.

from 21% from respective surgery to 50% from grafts plus barrier groups and probing depth reduction ranging from 33% from respective surgery to 48% from grafts plus barrier groups depending on the surgical therapy applied [14]. Therefore, the European Association for Osseointegration consensus stated that surgical therapy is superior to non-surgical therapy in resolving peri-implantitis [15]. However, its reported success rate was barely above 50% which might cast doubt on the benefit of the surgical methods despite its invasiveness. The outcomes were variable and influenced by factors not fully understood. In short, peri-implant lesions do not respond predictably to either nonsurgical or surgical treatments known so far [16]. Therefore, the currently proposed strategies for its treatment can be recognized as empirical [16]. Assuming that peri-implantitis is an infectious disease, the treatment strategy should reflect considerations on control of bacterial load in the oral cavity [12,17]. Some microbiologists claim that the peri-implantitis infection model can be classified as a non-specific plaque hypothesis [18]. Therefore, density of microorganisms can be an initiating factor, not a narrow range of microorganism types [19]. If this is the case, the treatment strategy should account for not only the infection, but also take into consideration the bacterial load of the entire mouth [20].

Sodium hypochlorite rinses have been of interest to clinicians for such a purpose. It has been demonstrated that the chemical sodium hypochlorite, which is frequently used in dentistry procedures, has antibacterial properties on a number of oral infection [21]. Gonzalez et al. performed an in vivo randomized controlled study to evaluate the clinical efficacy of sodium hypochlorite rinses for periodontitis patients, and the patients were instructed to rinse with 0.25% sodium hypochlorite twice per week for 30 s over the course of three months [22]. The authors suggested the result as additional evidence supporting an inter-relationship between supragingival plaque and subgingival plaque. Considering the promising findings of sodium hypochlorite treatment for periodontal lesions, the aim of this pilot study was to evaluate the feasibility of administering sodium hypochlorite oral rinses and analyze the clinical effects on peri-implantitis lesions.

2. Method

2.1. Ethical statement

This study was jointly conducted at the Department of Prosthodontics and Department of Periodontics, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea. The participants were included under informed consent according to the general guidelines of the Declaration of Helsinki, and the study was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital, The Catholic University of Korea (IRB no. KC17MESC0315, June 5, 2017).

2.2. Study design and inclusion criteria

Peri-implantitis sites exhibit clinical signs of inflammation, bleeding on probing, and/or suppuration, increased probing depths and/or recession of the mucosal margin in addition to radiographic bone loss [23] (Fig. 1A). The inclusion criteria for the presence of peri-implantitis include presence of bleeding on gentle probing and probing depths of $\geq$6 mm (Fig. 1B). As an open label pilot study, control group was not included. The individuals participated in the study without risking of receiving placebo. Since there was no information available from preceding research, it was determined that 12 subjects would be used as the pilot study [24,25]. The sample size was determined by considering a 90% power ($\alpha = 0.05$ and $1\text{-}\beta = 0.9$) with assumption of the intraclass correlation coefficient to be sufficiently small as 0.02. Test for two proportions in a cluster-randomized design was applied using proportions using commercially available program (PASS 13 program, NCSS Statistical Software, Kaysville, Utah, USA) and the minimum sample size was determined to be twelve. Twelve peri-implantitis patients were instructed to rinse with 15 mL of a fresh solution of 0.25% sodium hypochlorite for 30 s twice a week for 3 months (Fig. 1C). Clorox regular (Yuhan-Clorox Ltd., Yuhan Co, Ltd., Seoul, Korea) was used to prepare the solution and was diluted with distilled water in provided single-use bottles. A total of 24 bottles of 15 ml of 0.25% sodium hypochlorite was provided to each individual.

2.3. Peri-implant clinical parameters

Regardless of the number of existing peri-implantitis lesions, only 1 lesion was chosen for the test in terms of severity in probing depth. At baseline and 3-month visits, probing depth and gingival bleeding index were recorded at 6 points per lesion (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual). The following modified sulcular bleeding index was used to evaluate the marginal mucosal conditions around the dental implants [26,27]. Zero represents no bleeding when a periodontal probe is passed along the mucosal margin adjacent to the implant. A score of one indicates isolated bleeding spots. A score of two indicates that blood forms a confluent red line on the mucosal margin. A score of three indicates heavy or profuse bleeding.

2.4. Evaluation of bacterial loads

Individual and total bacterial loads of 18 pre-designated species of microorganisms were analyzed by real-time polymerase chain reaction (PCR) methods (Fluorescent reporter probe method, YD Global Life Science Co. Ltd., Seongnam-si, Gyeonggi-do, Korea) at baseline and 3-month visits. The participants were instructed to orally rinse with the gargling solution provided from the laboratory, and the solution was sent to the lab for bacterial load analysis. Eighteen pre-designated species of oral microorganisms and their abbreviations were: Aa (Aggregatibacter actinomycetemcomitans), Pg (Porphyromonas gingivalis), Tf (Tannerella forsythia), Td (Treponema denticola), Pi (Prevotella intermedia), Fn (Fusobacterium nucleatum), Pm (Parvimonas micra), Cr (Campylobacter

rectus), Pn (Prevotella nigrescens), En (Eubacterium nodatum), Ec (Eikenella corrodens), Sm (Strepotococcus mitis), Smu (Streptococcus mutans), Ss (Streptococcus sobrinus), Lc (Lactobacillus casei), Sa (*Staphylococcus aureus*), Ef (Enterococcus Faecalis), and Av (Actinomyces viscosus). Table 1 shows the information on primers used in this study. The samples were amplified using the following conditions: initial denaturation for 10 mintes at 95 °C and 40 cycles of 15 s at 95 °C, 40 s at 63 °C.

2.5. Statistical analysis

Each value is displayed as the mean minus the standard deviation. The examined data of probing depth, gingival bleeding, and bacterial counts were tested for normality and statistically analyzed using either the paired T test or Wilcoxon signed rank test depending on normality of the data.

3. Results

A total of 12 individuals participated in this study and had an average age of 63.8 years (Table 2). Of the 12 participants, 4 were males and 8 were females. The participants were instructed to visit the clinic after 12 weeks but the participation period varied according to duration of healing before follow-up visit to the clinic. The average period was 93.7 days.

The probing depth measurements and bleeding on probing indexes of the peri-implantitis involved lesions were recorded at baseline and final visits (Table 3). In 3 individuals the bleeding on probing indexes of the lingual surfaces were not measured and were treated as missing values during the experimental process. In general, statistically significant decrease of probing depth was noticed. The average difference was 1.1 mm with a standard deviation of 1.7 mm. Moreover, significant differences were noted in distobuccal, mesiolingual, lingual, and distolingual sites ($P < 0.05$).

Modified sulcular bleeding index decreased after the experiment (Table 4). The index decreased by a mean value of 0.8 with a standard deviation of 1.1. In detail, significant differences were noted in mesiobuccal, buccal and distobuccal sites ($P < 0.05$).

The results of the individual and total bacterial loads are shown in Table 5. The total bacterial loads were decreased after the treatment. In general, individual bacterial loads were decreased but this did not reach the statistical significance. Among the examined bacterial species, Ef and Av were not detected in any participants.

Table 1
Information on primers used in this study.

Primer	Sequence
Aggeregatibacter Actinomycetemcomitans (Aa)	forward, 5'-CGGGGCTTTCTACTACGGGA-3' reverse, 5'-ATGCCTCAAGCATTCTCGCA-3'
Porphyromonas gingivalis (Pg)	forward, 5'-ACACGGTGTATCGTGACGGC-3' reverse, 5'-GCCGGCTGCGTACTTAACCT-3'
Tanerella forsythensis (Tf)	forward, 5'-TGGCAAATCGCTCATCATCC-3' reverse, 5'-TTCCATGTTCCCCAACCACA-3'
Treponema denticola (Td)	forward, 5'-AGAAAGGCTTTGGGCGACAG-3' reverse, 5'-GCTGGAGCCGTAGCTTCCAT-3'
Fusobacterium nucleatum (Fn)	forward, 5'-GGCTGTCGTCAGCTCGTGTC-3' reverse, 5'-CTCATCGCAGGCAGTATCGC-3'
Prevotella intermedia (Pi)	forward, 5'-CACACGCTGGCGAAACCTAC-3' reverse, 5'-CACGTGGCGTTGCTTCTTTC-3'
Prevotella nigrescens (Pn)	forward, 5'-AGCAAGCTGTAGGCGAGGCT-3' reverse, 5'-GCTGAACACTTTCGCGTGCT-3'
Parvimonas micra (Pm)	forward, 5'-GAGGAATACCGGTGGCGAAG-3' reverse, 5'-GGCACCGAGATTTGACTCCC-3'
Campylobacter rectus (Cr)	forward, 5'-AAATTTAAGCGGCGACGAGG-3' reverse, 5'-TCCTTGCTCACGCTTACGGA-3'
Eubacterium nodatum (En)	forward, 5'-TGCTTGCCGGTGACTTAGGA-3' reverse, 5'-AAACCGGGCTCAACAACCAT-3'
Eikenella corrodens (Ec)	forward, 5'-GCCAACTGCTGCTGGAAGTG-3' reverse, 5'-GCCGCTGATTTCGGAGAGTT-3'
Streptococcus mitis (Sm)	forward, 5'-GTACAACGAGTCGCAAGCCG-3' reverse, 5'-TACAAGGCCCGGGAACGTAT-3'
Streptococcus mutans (Smu)	forward, 5'-CAGCGCATTCAACACAAGCA-3' reverse, 5'-TGTCCCATCGTTGCTGAACC-3'
Streptococcus sobrinus (Ss)	forward, 5'-GGCCTCATGCTGATTTTCCC-3' reverse, 5'-ACCACCACCCAGAAAATGGG-3'
Lactobacillus casei (Lc)	forward, 5'-CAACTGATCGTGCCAAGGGT-3' reverse, 5'-ACAGCGATTGGCAACAGACC-3'
Staphylococcus aureus (Sa)	forward, 5'-GCGCAAGTAACGAAAGCAAAA-3' reverse, 5'-GATTTTGCGCCACACTCGTT-3'
Enterococcus faecalis (Ef)	forward, 5'-GATGGCAGTGCGACACCATT-3' reverse, 5'-CGATCGTTTTGTTTGCCGAC-3'
Actinomyces viscosus (Av)	forward, 5'-GCTCCCTCATGCTCAACTCG-3' reverse, 5'-GATGATCTGGGCGTTGTCCA-3'

Table 2
Age, sex, and participation period of the participants.

Variable	Age (years)	Sex (male/female)	Periods (days)
Mean ± standard deviation	63.8 ± 13.1	Male: 4 Female: 8	93.7 ± 14.2

Table 3
Periodontal probing depth at baseline and follow-up evaluation.

Location	Periodontal probing depth			*P*-value
	Baseline	Follow-up	Differences	
MB	4.9 ± 1.8	4.0 ± 0.9	−0.9 ± 1.8	>0.05
B	5.3 ± 2.2	4.1 ± 0.9	−0.12 ± 2.0	>0.05
DB	6.4 ± 1.8	4.9 ± 1.9	−1.5 ± 1.8	<0.05
ML	5.5 ± 1.4	4.5 ± 1.4	−1.0 ± 1.2	<0.05
L	5.3 ± 0.9	4.3 ± 1.2	−1.0 ± 1.1	<0.05
DL	6.1 ± 1.1	4.8 ± 1.2	−1.3 ± 1.6	<0.05
Total	5.6 ± 1.7	4.4 ± 1.3	−1.1 ± 1.7	<0.05

Table 4
Differences in peri-implant parameter of modified sulcular bleeding index between baseline and follow-up.

Location	Modified sulcular bleeding index			*P*-value
	Baseline	3 months	Differences	
MB	1.5 ± 0.9	0.5 ± 0.8	−1.0 ± 0.9	<0.05
B	1.5 ± 0.9	0.7 ± 0.8	−0.8 ± 0.9	<0.05
DB	1.7 ± 0.6	0.9 ± 0.9	−0.8 ± 0.8	<0.05
ML	1.3 ± 0.8	0.8 ± 0.9	−0.4 ± 1.3	>0.05
L	1.2 ± 0.9	0.4 ± 0.7	−0.6 ± 1.2	>0.05
DL	1.7 ± 0.5	1.0 ± 0.8	−0.5 ± 0.8	>0.05
Total	1.5 ± 0.8	0.7 ± 0.8	−0.8 ± 1.0	<0.05

Table 5
The results of the total bacterial loads at baseline and follow-up.

Type	Bacterial loads (copies)			*P*-value
	Baseline	3 months	Differences	
Aa	4,286 ± 7,853	2,053,808 ± 15,256,448	4,464,150 ± 32,617,569	>0.05
Pg	11,295,867 ± 48,753,329	6,413,137 ± 26,196,978	1,664,849 ± 8,574,081	>0.05
Tf	9,717,210 ± 40,626,645	5,392,246 ± 28,410,119	8,035,321 ± 39,366,401	>0.05
Td	3,216,971 ± 16,334,624	22,367 ± 45,893	−255,450 ± 804,534	>0.05
Fn	3,206,252 ± 4,613,351	676,064 ± 1,279,944	−1,854,132 ± 5,235,097	>0.05
Pi	154,028 ± 515,643	466,097 ± 1,183,772	676,152 ± 1,617,961	>0.05
Pn	60,789 ± 93,052	23,642 ± 50,693	−3,962 ± 84,7540 ± 0	>0.05
Pm	48,201 ± 45,662	27,271 ± 40,892	6,334 ± 72,745	>0.05
Cr	9,244 ± 17,265	9,370 ± 24,114	2,586 ± 23,859	>0.05
En	2,557 ± 8,479	43,123 ± 214,023	49,289 ± 231,270	>0.05
Ec	129 ± 428	676 ± 2,141	547 ± 2,223	>0.05
Sm	4,836,467 ± 5,100,313	1,812,674 ± 1,254,087	−3,023,793 ± 5,385,431	>0.05
Smu	1,947,566 ± 2,840,276	427,318 ± 694,549	−1,520,247 ± 2,804,434	>0.05
Ss	48,904 ± 105,624	6,052 ± 19,368	−42,851 ± 107,343	>0.05
Lc	1,545 ± 2,993	1,859 ± 5,391	314 ± 6,395	>0.05
Sa	0 ± 0	2,964 ± 9,831	2,964 ± 9,831	>0.05
Ef	0 ± 0	0 ± 0	0 ± 0	>0.05
Av	0 ± 0	0 ± 0	0 ± 0	>0.05
Total	161,359,812.7 ± 103,432,233.0	114,787,426.3 ± 66,373,798.8	−46,572,386.3 ± 93,136,176.0	>0.05

Abbreviation: Aa (Aggregatibacter actinomycetemcomitans), Pg (Porphyromonas gingivalis), Tf (Tannerella forsythia), Td (Treponema denticola), Pi (Prevotella intermedia), Fn (Fusobacterium nucleatum), Pm (Parvimonas micra), Cr (Campylobacter rectus), Pn (Prevotella nigrescens), En (Eubacterium nodatum), Ec (Eikenella corrodens), Sm (Strepotococcus mitis), Smu (Streptococcus mutans), Ss (Streptococcus sobrinus), Lc (Lactobacillus casei), Sa (*Staphylococcus aureus*), Ef (Enterococcus Faecalis), and Av (Actinomyces viscosus).

4. Discussion

This study showed positive results of administering sodium hypochlorite oral rinse on peri-implantitis lesions regarding the reduction of periodontal probing depth and gingival bleeding index.

Sodium hypochlorite has been applied in various applications due to its antiseptic effects [28–31]. Application of sodium hypochlorite and sodium hydroxide was effective in preventing transmission of Creutzfeldt-Jakob disease through contaminated wires implanted into animal brains [32]. To investigate microbial colonization on reusable pneumatic tourniquets, postoperative tourniquets were wiped with a cloth soaked in sodium hypochlorite [33]. Sodium chlorite has been used for denture cleaning solutions [28]. The effect of cleaning methods on the retentive values of saliva-contaminated implant-supported zirconia copings was evaluated, and it was suggested that the restorations can be cleaned with sodium hypochlorite [29]. Sodium hypochlorite was applied against three peri-implantitis-associated microbiota strains (*Staphylococcus aureus*, Staphylococcus epidermidis, and Candida albicans) [30]. Moreover, sodium hypochlorite was used for recycling of implant healing abutments and resulted in no bacterial contamination [34]. Oral rinsing with sodium hypochlorite twice weekly was used as an available adjunct to conventional anti-plaque and anti-gingivitis treatments [31]. Sodium hypochlorite and minocycline in conjunction with ultrasonic debridement and soft tissue curettage led to synergistic effect on reduction of probing depth and bleeding on probing [35]. However, there are controversial results regarding the effects of sodium hypochlorite. The concomitant use of sodium hypochlorite with mechanical and chemical decontamination using titanium brushes and chlorhexidine during surgical treatment of peri-implantitis had a minor effect on treatment outcomes [36]. In a previous report, anti-infective therapy of peri-implant mucositis was evaluated with adjunctive delivery of a sodium hypochlorite gel, and addition of sodium hypochlorite gel with mechanical debridement did not produce statistically significant differences in peri-implant mucositis [37]. In this study, there were no signs of harmful effects on the recruited participants.

The effects of sodium hypochlorite concentration have been evaluated in previous studies [36,38–40]. A previous study used 2.5% sodium hypochlorite for reduction of contamination on used healing abutments and showed significantly greater effectivity than air polishing [41]. Another study used 1.0% sodium hypochlorite to disinfect customized abutments [42]. Similarly, 1% sodium hypochlorite was applied for the cleaning of zirconia copings [29]. This concentration of 1.0% sodium hypochlorite also was applied for cleaning of retentive attachments for dentures and demonstrated a significant in vitro effect on all three test microbes (Staphylococcus epidermidis, Candida albicans, and Streptococcus sanguinis) [38]. Biofilms grown on sandblasted, large-grit, acid-etched titanium discs were treated with a titanium brush with 1.0% sodium hypochlorite and 0.2% chlorhexidine [39]. For an in vitro study evaluating the effects of chemical agents on removal of Porphyromonas gingivalis and *Escherichia coli* from sandblasted acid-etched titanium dental implants, 1.3% sodium hypochlorite and 0.2% chlorhexidine were used [43]. The combination of 0.95% hypochlorite and 1 mg minocycline hydrochloride was used for the treatment of peri-implantitis along with a nonsurgical treatment [35]. Also, 0.125%, 0.25%, and 0.5% sodium hypochlorite were used for wound irrigation after surgical debridement for orthopedic infections [44]. Oral rinsing with 0.1%–0.25% sodium hypochlorite was used to improve periodontal health [31]. A 0.25% solution of sodium hypochlorite has been used for decontamination of dental implant surfaces after mechanical treatment with plastic curettes [40]. Application of 0.1% sodium hypochlorite produced a significant bactericidal effect against adhering bacteria after in vivo biofilm formation on titanium specimens fixed to individual removable acrylic upper jaw splints [45]. In a different study, 0.1% sodium hypochlorite was concomitantly used with a titanium brush and chlorhexidine for decontamination purposes during surgical peri-implantitis treatment [36].

Application time varied among studies [42,44,46]. For wound irrigation after surgical debridement for orthopedic infections, sodium hypochlorite was applied for 1, 5, and 10 min [44]. Sodium hypochlorite was applied for 5 min to disinfect customized abutments [42]. To evaluate the efficacy of antibacterial sealing gel, 2% sodium hypochlorite solution was applied for 30 min [46]. Sodium hypochlorite was applied for 1 min to clean the retentive attachments in dentures [38]. Sodium hypochlorite was applied for 1 min for antibacterial effects on a titanium surface [45].

The American Dental Association Council on Dental Therapeutics classified 0.1% sodium hypochlorite as a mild antiseptic mouth rinse [47–49]. In a previous report, 5 mL of 5%–6% standard household bleach was combined with sterile water to form a 0.25% solution of sodium hypochlorite [40]. As in a previous report, sodium hypochlorite solution was created from a commercially available product. Sodium hypochlorite does not induce allergies; is not a carcinogen, teratogen, or mutagen; and has a long record of safety [47,50]. Clorox regular that contains 4% sodium hypochlorite is classified as a food additive by the Ministry of Food and Drug Safety of the Republic of Korea. Sodium hypochlorite solutions in the concentration range of 2%–8% did not produce significant differences in inflammatory response compared with sterile physiologic saline, which was derived from reactions of connective tissue exposure to sodium hypochlorite in an animal model [51].

Periodontitis can be mathematically modeled as a chaotic non-linear system [52]. From an infectious disease perspective, periodontitis and peri-implantitis can be regarded as complex systems that are characterized by non-linear inter-relationships of multiple variables [53]. Sodium hypochlorite rinses led to a reduction in bleeding on probing without mechanical and surgical debridement [22].

The present study contains several limitations. There was no control group against which to compare findings. In addition, lack of blinding in the study produced a risk of bias However, the positive results of this pilot trial confirmed the feasibility of large scale clinical trials in the future. In order to further validate the findings and evaluate the long-term effects of sodium hypochlorite oral rinse on peri-implantitis lesions, future perspectives for this study include conducting larger and more thorough clinical trials with a larger sample size, a control or placebo group, and longer follow-up periods.

5. Conclusions

This study suggested that the concentration of 0.25% be used for treatment of peri-implantitis. Given the lack of reliable treatment for peri-implantitis and the patient's reluctance to invasive treatment, this study served as a useful starting point for the research on novel non-invasive treatment method.

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Institutional Review Board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Seoul St. Mary's Hospital, The Catholic University of Korea (IRB no. KC17MESC0315, June 5, 2017).

Informed consent statement

Informed consent was obtained from all participants involved in the study.

Author contribution statement

Wonsup Lee and Jun-Beom Park: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data Availability statement

All data are contained within the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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