DOUTORADO EM ODONTOLOGIA

BERNAL STEWART

ESTUDO CLÍNICO ALEATORIZADO AVALIANDO OS EFEITOS DE UM DENTIFRÍCIO CONTENDO 0,3% DE TRICLOSAN NOS PARÂMETROS PERIODONTAIS E PERI-IMPLANTARES EM PACIENTES TRATADOS PARA PERI-IMPLANTITE E EM FASE DE MANUTENÇÃO: AVALIAÇÃO DE 2 ANOS.

Guarulhos

2017

BERNAL STEWART

ESTUDO CLÍNICO ALEATORIZADO AVALIANDO OS EFEITOS DE UM DENTIFRÍCIO CONTENDO 0,3% DE TRICLOSAN NOS PARÂMETROS PERIODONTAIS E PERI-IMPLANTARES EM PACIENTES TRATADOS PARA PERI-IMPLANTITE E EM FASE DE MANUTENÇÃO: AVALIAÇÃO DE 2 ANOS.

Tese apresentada à Universidade Guarulhos para obtenção
do título de Doutor em Odontologia
Área de Concentração: Periodontia
Orientadora: Prof[a]. Dr[a]. Magda Feres
Co-orientadora: Prof[a]. Dr[a]. Luciene Cristina de Figueiredo

Guarulhos

2017

Ficha catalográfica elaborada pelo Sistema de Bibliotecas Fernando Gay da Fonseca

S931e

Stewart, Bernal

Estudo clínico aleatorizado avaliando os efeitos de um dentifrício contendo 0,3% de triclosan nos parâmetros periodontais e peri-implantares em pacientes tratados para peri-implantite e em fase de manutenção: avaliação de 2 anos. / Bernal Stewart. -- 2017.

82 f.; 31 cm.

Orientador: Profª. Dr. Magda Feres

Tese (Doutorado em Odontologia) – Centro de Pós-Graduação e Pesquisa e Extensão, Universidade Guarulhos, Guarulhos, SP, 2017.

1. Peri-implantite 2. Triclosan 3. Cremes dentais 4. Terapêutica I Título II. Feres, Magda (Orientador). III. Universidade Guarulhos

CDD. 617.6

A Comissão Julgadora dos trabalhos de Defesa de Tese de DOUTORADO, intitulada "ESTUDO CLÍNICO ALEATORIZADO AVALIANDO OS EFEITOS DE UM DENTIFRÍCIO CONTENDO 0,3% DE TRICLOSAN NOS PARÂMETROS PERIODONTAIS E PERI-IMPLANTARES EM PACIENTES TRATADOS PARA PERI-IMPLANTITE E EM FASE DE MANUTENÇÃO: AVALIAÇÃO DE 2 ANOS" em sessão pública realizada em 15 de março de 2017 considerou o candidato Bernal Antonio Stewart Satchwell aprovado.

COMISSÃO EXAMINADORA:

1. Profa. Dra. Magda Feres (UNG)_____

2. Prof. Dr. Márcio Zaffalon Casati (UNIP)_____

3. Profa. Dra. Cristina Cunha Villar (FOUSP)_____

4. Profa. Dra. Poliana Mendes Duarte (UNG)_____

5. Prof. Dr. Jamil Awad Shibli (UNG)_____

Guarulhos, 15 de março de 2017.

DEDICATÓRIA

Dedico este trabalho à minha mãe, Eloisa Satchwell, ao meu pai Egbert Stewart, e a minha tia Virginia Hyman por seu apoio e exemplo.
Vocês me motivaram a alcançar meus sonhos.

Dedico esta tese também aos meus sobrinhos e sobrinhas, para que ela lhes sirva de inspiração. Espero que sempre sigam os seus sonhos.

Dedico esta tese também aos meus irmãos e suas esposas
pelo seu amor, apoio e por sempre lembrarem de mim em suas orações...

Amo todos vocês!

AGRADECIMENTOS

A Deus por sua orientação e proteção.

Aos meus pais, Eloisa e Egbert. Aos meus irmãos: Alvaro, Ignacio, Edgar, Francisco e Delano e às suas esposas. Aos meus sobrinhos e sobrinhas. À tia Vicky e minhas primas, Jennifer e Karen. À minha família e amigos pelo seu apoio incondicional em todas as fases da minha vida.

À Profa. Magda Feres, em primeiro lugar, muito obrigado por sua amizade e liderança e por ser uma grande mentora. Sua capacidade de motivar e inspirar as pessoas é sem limites. Não tenho palavras para expressar meu amor e admiração pelas coisas que você faz na escola, em casa e, pelos outros. O respeito e a dedicação que você tem com seu trabalho é um exemplo a seguir. Sua capacidade de superar obstáculos e, ainda inspirar as pessoas, é uma virtude que poucos têm. Quero agradecer-lhe, profundamente, por tudo o que você fez por mim.

À Profa. Luciene Figueiredo, minha co-orientadora, obrigado pelo ser humano que você é. Sua paciência, honestidade e integridade são um exemplo a ser seguido. Não importa quão ocupado tenha sido o seu dia, você sempre encontrou tempo para mim e meus colegas de classe. Eu agradeço-lhe por isso!

Ao Prof. Marcelo Faveri que, ao longo dos anos, se tornou um amigo, um professor e um parceiro de pesquisa. Muito obrigado pelo carinho, preocupação e exemplo de pessoa que demonstrou ser em todas as aulas e fora delas.

Aos meus professores: Jamil Shibli, Poliana Duarte, André Reis, Jose Augusto Rodrigues, Marta Bastos, Geisla Soares, e Alessandra Cassoni Ferreira. Muito obrigado pelo meu crescimento profissional e pessoal. Agradeço-lhes cada oportunidade que me proporcionaram para que eu pudesse aprender.

Ao Prof. Giuseppe A. Romito e sua família, sou eternamente agradecido pela amizade, carinho, preocupação e ajuda sem limites. Você não só abriu as portas de sua casa, mas também me acolhe como um irmão em sua vida. Muito obrigado!

À Belén, Flavia, Renata, Tatiana e Izilvânia, pelo profissionalismo e dedicação a esta pesquisa. Muito obrigado pela sua amizade e carinho.

Aos meus colegas de turma, agradeço-lhes pela preocupação, amizade e ajuda ao longo destes anos, igualmente, pela sua cumplicidade, apoio e carinho.

Ao Prof. Milton Silva e sua família, o Brasil não teria o mesmo sentido sem vocês ao meu lado. Desde minha primeira viagem ao Brasil, vocês se tornaram minha família.

Aos professores: Maurício Araujo, Cassiano Rösing, Enilson Sallum e Augusto Elias pelo apoio incondicional.

Aos meus queridos amigos: da Costa Rica, Brasil, Chile, Peru, Colombia, Mexico, Argentina, Canada, USA, Caribe, Camino de Santiago, Espanha, Alemanha e do Estanconfor (Bela Vista). Muito obrigado pelo apoio, amor e amizade.

À Bill De Vizio, Tony Volpe e minha família Colgate Palmolive, muito obrigado por me proporcionar as oportunidades para alcançar meus sonhos, crescer, ver o mundo, descobrir novas fronteiras, trabalhar com pessoas interessantes, poder ajudar outros a alcançarem os seus sonhos e ajudar a desenvolver a minha amada Latam.

À Samantha Carvalho, Maria Josefa Mestnik, Helio Doyle, Gabriela Giro Araújo, Bruno Bueno, Murilo Feres, Marina Roscoe e Maurilo Lemos por sua amizade e apoio.

As familias Feres, Romito, Figuereido, Faveri, Araujo, Rosing, Sallum, Cury, Antunes, Oliveira, Sintes, Elias, Ayad, e Silva; eternamente agradecido pela amizade, carinho, preocupação e ajuda sem limites.

Aos membros de Lantin America Oral Health Association (LAOHA); muito obrigado pelo apoio e amizade.

À Universidade Guarulhos e a todos os seus funcionários, principalmente aqueles do Centro de Pós-Graduação, Pesquisa e Extensão (CEPPE), por abrirem as portas para que eu pudesse aprender e crescer.

Ao Ministério da Educação e a Comissão de Aperfeiçoamento de Pessoal do Nível Superior (CAPES) pela concessão da bolsa de estudos.

A TODOS, MUITO OBRIGADO

É a arte suprema do professor,
despertar alegria na expressão criativa
e no conhecimento. –
Albert Einstein

RESUMO

O objetivo deste estudo foi avaliar os efeitos de um dentifrício contendo 0,3% de triclosan nos parâmetros peri-implantares e periodontais de pacientes tratados para peri-implantite que seguiram um programa regular de manutenção por dois anos. Indivíduos que apresentaram pelo menos um implante com peri-implantite e receberam tratamento cirúrgico anti-infeccioso foram incluídos no estudo. Sessenta dias depois do tratamento cirúrgico (início do estudo) os indivíduos foram distribuídos aleatoriamente em dois grupos: (i) dentifrício contendo 0,3% de triclosan + 2,0% de copolímero Gantrez + 1450 ppm de flúor (teste) ou (ii) dentifrício contendo 1450 ppm de flúor (controle), e instruídos a escovar os dentes, usando apenas o dentifrício alocado, duas vezes ao dia por dois anos. Todos os indivíduos retornaram para visitas de manutenção peri-implantar e periodontal a cada 3 meses e receberam instrução de higiene oral, raspagem supragengival e subgingival dos dentes e implantes, e profilaxia. Além disso, os indivíduos receberam monitoramento clínico e microbiológico no início do estudo e após 3, 6, 12, 18 e 24 meses. 102 indivíduos foram incluídos (teste, n = 48; controle, n = 54). O grupo controle apresentou perda de inserção clínica (IC) ao redor dos implantes tratados ao longo do estudo ($p<0,05$), enquanto que o grupo teste mostrou estabilidade para este parâmetro. A diferença entre os grupos para a alteração na IC entre o início do estudo e 24 meses (0,55 mm) foi estatisticamente significativa (variável primária). Os patógenos do complexo vermelho só foram reduzidos no grupo teste aos 24 meses ($p<0,05$). Os implantes sem histórico de peri-implantite mostraram uma redução significativa no percentual de sítios com sangramento à sondagem (SAS) e na média de profundidade de sondagem (PS) no grupo teste, ao longo do estudo ($p<0,05$). Essa melhora não foi observada no grupo controle. Em relação aos parâmetros periodontais, o grupo teste (n=39) apresentou maior redução no percentual de sítios com SAS e níveis mais baixos de placa em comparação ao grupo controle (n=49) após 24 meses de escovação ($p<0,05$). Apenas o grupo teste teve uma redução estatisticamente significativa na média percentual dos sítios periodontais com PS≥5 mm ao longo do estudo. Os dados do presente estudo mostraram que um dentifrício contendo 0,3% de triclosan foi mais eficaz do que um dentifrício regular fluoretado na manutenção da estabilidade clínica e de um perfil microbiano subgengival mais benéfico de implantes tratados para peri-implantite em indivíduos que seguiram um programa regular de manutenção por 2 anos. Além disso, o dentifrício contendo 0,3% de triclosan foi mais eficaz na manutenção de um ambiente mais saudável ao redor dos implantes sem histórico de peri-implantitie e dos dentes naturais.

Palavras-chave: Peri-implantite, Triclosan, Cremes Dentais, Terapêutica, Doenças Periodontais, Periodontite, Dentifrício.

ABSTRACT

The aim of this study was to evaluate the effects of a dentifrice containing 0.3% triclosan on peri-implant and periodontal parameters of subjects treated for peri-implantitis that were enrolled in regular maintenance program for two years. Subjects presenting at least one implant with peri-implantitis received surgical anti-infective therapy and were enrolled in the study. Sixty days after surgery (baseline), subjects were randomized into two groups: (i) toothpaste containing 0.3% triclosan + 2.0% Gantrez copolymer + 1450 ppm fluoride (test) or (ii) toothpaste containing 1450 ppm fluoride (control), and instructed to brush their teeth with the assigned toothpaste twice a day for two years. All subjects returned for the maintenance visits every 3 months and received oral health instructions, supragingival and subgingival biofilm removal from teeth and implants, and a prophylaxis. In addition, they received clinical and microbiological monitoring at baseline and at 3, 6, 12, 18 and 24 months. 102 subjects were enrolled in the study (test, n=48; control, n=54). The control group exhibited loss of clinical attachment (CA) around the treated implants over the course of the study ($p<0.05$), while the test group showed stability for this parameter. The difference between groups for CA change between baseline and 24 months (0.55 mm) was statistically significant (primary outcome variable). The red complex pathogens were only reduced in the test group at 24 months ($p<0.05$). The implants with no history of peri-implantitis had a significant reduction in the percentage of sites with bleeding on probing (BOP) and in mean probing depth (PD) in the test group, throughout the study ($p<0.05$). This improvement was not observed in the control group. Regarding the periodontal parameters, the test group (n=39) had a greater reduction in the percentage of sites exhibiting BOP and lower levels of plaque in comparison with the control group (n=49) after 24 months of brushing with the assigned toothpastes ($p<0.05$). The mean percentage of sites with PD≥ 5mm was reduced over the course of the study only in the test group ($p<0.05$). The data of the present study showed that a toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining peri-implant clinical stability and a more beneficial subgingival microbial profile around implants treated for peri-implantitis in subjects who were enrolled in a regular maintenance program for 2 years. In addition, a toothpaste containing 0.3% triclosan was more effective in maintaining a healthier environment around implants with no history of peri-implantitis and natural teeth.

Key-words: Peri-implantitis, Triclosan, Toothpastes, Therapeutics, Periodontal diseases, Periodontitis, Dentifrices.

LISTA DE FIGURAS

Artigo 1

Figure 1 *Study Flow Chart.* 42

Figure 2.a *Line chart of mean changes in Clinical Attachment and Probing Depth for treated implants and implants with no history of peri-implantitis between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent p<0.05), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (*p<0.05).* 46

Figure 2.b *Line chart of mean changes in Plaque Index, Gingival Index and Bleeding on Probing for treated implants and implants with no history of peri-implantitis between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent p<0.05), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* p<0.05).* 47

Figure 3 *Line chart of the mean Bone Height over the course of the study and mean changes in this parameter from baseline to all follow-up time points. The blue line represents the test group and the red line represents the control group. The significance of differences within each group for mean levels of bone height and the changes between baseline and the other time-points was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center ($p<0.05$).* 48

Figure 4 *Pie charts of the mean proportions of each microbial complex in the subgingival plaque samples for treated implants. Different colors represent the microbial complexes described by Socransky et al. (1998). The grey color ('Others') represents species that did not fall into any complex, and Actinomyces spp. are represented in blue. Significance of differences in mean proportions between baseline and 24 months was sought using Wilcoxon Test (** $p<0.001$) and between groups at each time point using the Mann–Whitney U-test ($p>0.05$).* 51

Artigo 2

Figure 1	*Study Flow Chart.*	69
Figure 2.a	*Line chart of mean changes in Bleeding on Probing, Plaque Index and Gingival Index between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent p<0.05), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* p<0.05).*	71
Figure 2.b	*Line chart of mean changes in Probing Depth and Clinical Attachment between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent p<0.05), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* p<0.05).*	72

LISTA DE TABELAS

Artigo 1

Table 1	*Baseline data and demographic characteristics of the population studied, stratified per group.*	43
Table 2	*Mean clinical parameters at Pre-baseline and at Baseline, and mean changes in these parameters between the two time-points.*	44
Table 3	*Mean (± SEM) values for clinical parameters over the course of the study.*	45
Table 4	*Mean % (± SD) sites gaining or loosing ≥ 2mm of Clinical Attachment (CA) between baseline and the follow-up appointments.*	49
Table 5	Mean (± SEM) % of sites for treated implants in different Probing Depth (PD) categories over the course of the study.	50

Artigo 2

Table 1	*Mean (± SD) number (and percentage) of subjects presenting different numbers of sites with probing depth (PD) and clinical attachment level (CAL)≥5mm at pre-baseline and baseline time-points, and mean number (± SD) of sites with PD and CAL ≥ 5 mm at each time point.*	70
Table 2	*Mean (± SEM) values for clinical parameters over the course of the study.*	73
Table 3	*Mean (± SEM) values for probing depth (PD) over the course of the study.*	74
Table 4	*Clinical relevance assessment for the effects of different toothpastes on "mean reduction in the percentage of sites with bleeding on probing from baseline to 24 months".*	75

LISTA DE ABREVIATURAS E SIGLAS

ppm	Partes Por Milhão / *Parts-Per Million*
NCI	Nível Clínico de Inserção
mm	Milímetro / *Millimeter*
p	Valor p / *p-value*
SAS	Sangramento à Sondagem
PS	Profundidade de Sondagem
CAL	*Relative Clinical Attachment Level*
RCT	*Randomized Clinical Trial*
CA	*Clinical Attachment*
CAL	*Clinical Attachment Level*
PD	*Probing Depth*
BOP	*Bleeding On Probing*
OHI	*Oral Hygiene Instructions*
CAAE	Certificado de Apresentação para Apreciação Ética
e.g.	*For example*
PI	*Plaque Index*
GI	*Gingival Index*
SEM	*Standard Error of the Mean*
MPE	*Mean Percentage Error*
ml	Mililitro
HCl	Ácido Clorídrico
mM	Milimolar
EDTA	*Ethylenediamine tetraacetic acid*
pH	Potencial Hidrogeniônico
M	*Molar*
NaOH	Hidróxido de sódio
DNA	*Deoxyribonucleic Acid*
SRP	*Scaling and Root Planing*
ES	*Effect Sizes*
MID	*Minimal Important Differences*

LISTA DE SÍMBOLOS

%	Percentual
<	Menor que
≥	Maior ou igual a
=	Igual a
+	Mais
α	Alfa
#	Número
~	Aproximadamente

SUMÁRIO

		Página
1.	**INTRODUÇÃO E JUSTIFICATIVA**……..	18
2.	**PROPOSIÇÃO**…….	23
3.	**ARTIGOS CIENTÍFICOS** ……...	24
3.1	**Artigo 1: Effects of a toothpaste containing 0.3% triclosan in the maintenance phase of peri-implantitis treatment: 2-year randomized clinical trial** ……	24
3.2	**Artigo 2: Effects of a toothpaste containing 0.3% triclosan in the periodontal parameters of subjects with history of peri-implantitis enrolled in a regular maintenance program: a secondary analysis of a 2-year randomized clinical trial** …….	52
4.	**CONCLUSÃO** ……	76
	REFERÊNCIAS …….	77

1. INTRODUÇÃO E JUSTIFICATIVA

Com o aumento do uso de próteses implanto-suportadas que ocorreu principalmente nas duas últimas décadas, problemas associados aos tecidos peri-implatares têm sido observados com mais frequência. As duas formas mais comuns de doenças peri-implantares são a mucosite e a peri-implantite (LINDHE & MEYLE, 2008). A mucosite peri-implantar tem sinais clínicos semelhantes aos da gengivite, como por exemplo, vermelhidão e/ou edema dos tecidos moles ao redor do implante, e sangramento marginal e/ou à sondagem. Além disso, como na gengivite, na mucosite tambem não há perda do tecido ósseo de suporte associada (MOMBELLI & LANG, 1998; LINDHE & MEYLE, 2008; ZITZMAN & BERGLUNDH, 2008; RAMANAUSKAITE & JUODZBALYS, 2016). A peri-implantite pode estar associada com sangramento à sondagem, supuração e bolsas profundas. Porém, o sinal patognomônico dessa condição é a perda do osso marginal de suporte de um implante em função (MOMBELLI & LANG, 1998; LINDHE & MEYLE, 2008; ZITZMAN & BERGLUNDH, 2008; RAMANAUSKAITE & JUODZBALYS, 2016). Embora os implantes dentários tenham uma taxa de sucesso elevada, a prevalência de peri-implantite tem aumentado mundialmente (ZITZMAN & BERGLUNDH, 2008; MOMBELLI et al., 2012; DERKS & TOMASI, 2015; DERKS et al., 2016; SALVI et al., 2017). Numa revisão sistemática recente foi relatado que a prevalência de mucosite peri-implantar e peri-implantite varia de 19% a 65% e de 1% a 47%, respectivamente, em pacientes portadores de implantes. As meta-análises estimaram prevalências médias ponderadas de mucosite peri-implantar e peri-implantitis de 43% e 22%, respectivamente (DERKS & TOMASI, 2015).

As doenças peri-implantares são infecções complexas causadas por patógenos orais que colonizam a cavidade oral, em geral os mesmos observados nas doenças periodontais. Uma revisão sistemática recente sugeriu uma associação entre reconhecidos patógenos periodontais, tais como *Porphyromonas gingivalis*, *Treponema denticola* e *Tannerella forsythia* e a peri-implantite (PÉREZ-CHAPARRO et al., 2016). Aparentemente, a etiopatogênese das periodontites e peri-implantites também é semelhante. A microbiota patogênica peri-implantar é capaz de produzir

endotoxinas, que induzem a secreção de citocinas e quimiocimas, aumentando o infiltrado inflamatório e a liberação de enzimas proteolíticas responsáveis pela destruição dos tecidos peri-implantares (MOMBELLI & LANG, 1998; MOMBELLI, 1999; KIVELA-RAJAMAKI et al., 2003).

Devido a natureza infecciosa, o tratamento da peri-implantite deve incluir medidas anti-infecciosas (KLINGE et al., 2002; LINDHE & MEYLE, 2008). Os tratamentos mais comumente utilizados para o re-estabelecimento da saúde e da arquitetura dos tecidos peri-implantares podem ser químicos (MOMBELLI et al., 2001), físicos (HASS et al., 2000; SCHWARZ et al., 2005; SHIBLI et al., 2006), não-cirúrgicos (MOMBELLI et al., 2001; FERRARI, 2008), cirúrgicos associados à regeneração óssea guiada e/ou biomateriais (HÄMMERLE et al., 1995; KHOURY & BUCHMANN, 2001) ou uma combinação destas terapias (BEHNEKE et al., 2000; ROMEO et al., 2004; ROOS-JANSAKER et al., 2007). Estas estratégias terapêuticas têm em comum três finalidades distintas: a descontaminação da superfície do implante, reestablecimento da saude dos tecidos peri-implantares e a restauração da arquitetura peri-implantar (KLINGE et al., 2002; ROOS-JANSAKER et al., 2003; HEITZ-MAYFIELD & MOMBELLI, 2014). Os estudos realizados em animais (ERICSSON et al., 1996; SCHOU et al. 2003; SHIBLI et al., 2003; SHIBLI et al., 2006) e alguns estudos clínicos em seres humanos (HÄMMERLE et al., 1995; BEHNEKE et al., 2000; HASS et al., 2000; KHOURY & BUCHMANN, 2001; MOMBELLI et al., 2001; ROMEO et al., 2004; SCHWARZ et al., 2005) mostram que o principal fator que determina o aumento do percentual de preenchimento ósseo é a descontaminação de toda a área peri-implantar associada à supressão dos patógenos periodontais (HÄMMERLE et al., 1995; BEHNEKE et al., 2000; HASS et al., 2000; KLINGE et al., 2002; ROOS-JANSAKER et al., 2003; SHIBLI et al., 2003; LINDHE & MEYLE, 2008).

Após a fase de tratamento ativo, assim como no caso das periodontites, é fundamental que os pacientes entrem em fase de manutenção. Sabe-se que um dos principais indicadores de risco para a peri-implantite é a higiene oral deficiente (LINDHE & MEYLE, 2008), logo, o sucesso do tratamento está diretamente relacionado ao controle do biofilme supragengival durante as fases de recolonização

microbiana e manutenção periodontal. Vários métodos, incluindo o uso de escovas dentais e interdentais são normalmente recomendados para o controle mecânico do biofilme dental, no entanto, a maioria dos pacientes não é capaz de realizar de maneira satisfatória a remoção deste biofilme (CUMMING & LÖE, 1973; TONETTI et al., 2015). Uma justificativa para este fato é a falta de destreza manual e a pouca cooperação dos indivíduos (WILSON, 1987).

Diversos produtos de higiene bucal têm sido utilizados como adjuntos ao métodos mecânicos tradicionais de controle do biofilme oral, na tentativa de otimizar a saúde oral, tanto em pacientes com saúde periodontal e peri-implantar, quanto naqueles com periodontite e peri-implantite, nas fases de tratamento e/ou manutenção (MORAN et al., 1991; JENKINS et al., 1993; YATES et al., 1993; KJAERHEIM et al., 1996; BOTUSHANOV et al., 2001; ARCHILA et al., 2005; MULLER et al., 2006; MATEU et al., 2008; RAMBERG et al., 2009; BONETA et al., 2010; DE ANDRADE MEYER et al., 2010; MANKODI et al., 2011; PRADEEP et al., 2012; COSTA et al., 2013; RILEY & LAMONT, 2013; KANG et al., 2015; TRIRATANA et al., 2015). Esses produtos, normalmente dentifrícios ou enxaguatórios, são encontrados nas prateleiras de supermercados, lojas de cosmético e farmácias e podem conter os mais variados ingredientes ativos. Para ser empregado na cavidade oral, um medicamento deve apresentar basicamente as seguintes propriedades: (1) segurança, que corresponde à incapacidade de induzir reações alérgicas e toxicidade; (2) sabor agradável e facilidade de manipulação; (3) efetividade, que consiste na capacidade de reduzir o biofilme dental e a gengivite; (4) especificidade para a microbiota periodontopatogênica e/ou cariogênica; (5) substantividade, que constitui na permanência do agente nas estruturas bucais por um longo período de tempo (VAN DER OUDERAA, 1991).

Existem vários veículos para a liberação dos agentes antimicrobianos na cavidade oral como colutórios, dentifrícios, géis, vernizes e dispositivos de liberação lenta. O veículo ideal deve reunir características como a sua compatibilidade com o agente ativo, uma adequada biodisponibilidade do agente ativo no local de ação, além de uma boa aceitação por parte do paciente. A seleção do veículo mais apropriado vai depender das necessidades individuais de cada paciente, assim

como da comodidade de sua utilização. Para casos que necessitam de um efeito em toda a cavidade oral, como aqueles pacientes em manutenção periodontal/peri-implantar, os dentifrícios e colutórios são os mais indicados (CUMMINS & CREETH, 1992). Os dentifrícios possuem a vantagem de não exigirem mudanças de hábitos por parte do paciente, garantindo um alto grau de cooperação (CURY & TENUTA, 2014).

Um dos mais bem aceitos antimicrobianos e com eficiência reconhecida pela literatura é o triclosan. Sua ação baseia-se na desorganização da membrana celular bacteriana e inibição inespecífica de enzimas da membrana. O triclosan possui amplo espectro antimicrobiano, com atividade contra bactérias Gram-positivas, Gram-negativas e fungos. Ele inibe a incorporação e metabolismo da glicose por *Streptococcus mutans, Streptococcus sanguis e Actinomyces naeslundii*, e a atividade de proteases tipo tripsina de *P. gingivalis* e *Capnocytophaga gingivalis* (FINE et al., 1998; XU et al., 2005; HARASZTHY et al., 2010). Além disso, o triclosan tem efeito anti-inflamatório (GAFFAR et al., 1995; MODEER et al. 1996, PANAGAKOS et al. 2005).

O triclosan pode ser encontrado no mercado, para uso odontológico, como integrante de colutórios ou dentifrícios, normalmente em concentração de 0,2 a 0,3%. Uma recente revisão sistemática da "*The Cochrane Collaboration*" (RILEY & LAMONT, 2013) reuniu todas as evidências disponíveis na literatura sobre os efeitos a longo prazo dos dentifrícios contendo triclosan no controle de cárie, gengivite e biofilme dental. Os autores mostraram evidência moderada para o efeito desses dentifrícios na redução do biofilme dental e inflamação gengival, quando comparado ao efeito obtido com o uso de dentifrícios contendo flúor, sem triclosan. Os poucos estudos que avaliaram os efeitos de dentifrícios contendo triclosan em pacientes com histórico de periodontite, não-fumantes (ROSLING et al., 1997; ELLWOOD et al., 1998; CULLINAN et al., 2003) ou fumantes (KERDVONGBUNDIT & WIKESJÖ et al., 2003) mostraram um benefício desses dentifrícios no ganho clínico de inserção e na redução do sangramento à sondagem. Porém, nenhum desses estudos incluiu um programa regular de manutenção periodontal com intervenções profissional supra e subgengival em intervalos regulares. Em relação aos implantes dentais, dois

estudos com avaliação de 6 meses mostraram efeitos benéficos com o uso de dentifrícios contendo triclosan, em comparação a dentifrícios controles, em pacientes apresentando pelo menos um implante em função (SREENIVASAN et al., 2011) ou mucosite (RAMBERG et al., 2009). Porém, nenhum estudo até hoje avaliou os efeitos de dentifrícios contendo triclosan ou outro antimicrobiano após tratamento da peri-implantite.

Tendo em vista a escassez de dados longitudinais na literatura sobre os efeitos do dentifrício contendo triclosan em parâmetros periodontais e peri-implantares, a condução de estudos nessa área pode trazer importantes contribuições para essa área do conhecimento.

2. PROPOSIÇÃO

O objetivo deste estudo clínico aleatorizado foi avaliar os efeitos de um dentifrício contendo 0,3% de triclosan em pacientes tratados para peri-implantite e que seguiram um programa de manutenção peri-implantar e periodontal por 2 anos:

1- Nos parâmetros clínicos (objetivo principal) e microbiológicos ao redor dos implantes tratados para peri-implantite;

2- Nos parâmetros clínicos ao redor dos implantes sem histórico de peri-implantite;

3- Nos parâmetros clínicos periodontais ao redor dos dentes naturais.

3. ARTIGOS CIENTÍFICOS

3.1 Artigo 1

Artigo cientifico a ser submetido na revista científica *Clinical Oral Implant Research*

EFFECTS OF A TOOTHPASTE CONTAINING 0.3% TRICLOSAN IN THE MAINTENANCE PHASE OF PERI-IMPLANTITIS TREATMENT: 2-YEAR RANDOMIZED CLINICAL TRIAL

Bernal STEWART[1,3], Jamil A. SHIBLI[1], Mauricio ARAUJO[2], Luciene Cristina FIGUEIREDO[1], Fotinos PANAGAKOS[3], Flavia MATARAZO[2], Renata MAIRINK[1], Tatiana ONUMA[1], Marcelo FAVERI[1], Belén RETAMAL-VALDES[1], Magda FERES[1]

[1] Department of Periodontology, Dental Research Division, Guarulhos University, Guarulhos, São Paulo, Brazil

[2] School of Dentistry, State University of Maringa, Maringa, Paraná, Brazil

[3] Colgate-Palmolive Technology Center, Piscataway, New Jersey, USA

Address for correspondence and reprints **(e-mail can be published)**

Bernal Stewart

909 River Road

Piscataway, New Jersey 08873

Phone: +1-732-878-7597

E-mail: bernal_stewart@colpal.com

EFFECTS OF A TOOTHPASTE CONTAINING 0.3% TRICLOSAN IN THE MAINTENANCE PHASE OF PERI-IMPLANTITIS TREATMENT: 2-YEAR RANDOMIZED CLINICAL TRIAL

ABSTRACT

Aim: To evaluate the effects of a toothpaste containing 0.3% triclosan of patients that have been treated for peri-implantitis and were enrolled in a maintenance program. **Methods**: Subjects presenting at least one implant with peri-implantitis and received surgical anti-infective therapy were selected. Sixty days post-surgery (baseline), subjects were randomized into two groups: (i) toothpaste containing 0.3% triclosan + 2.0% Gantrez copolymer + 1450 ppm fluoride (test) or (ii) toothpaste containing 1450 ppm fluoride (control), and were instructed to brush with the assigned toothpaste twice/day for 2 years. They received clinical and microbiological monitoring at baseline, 3, 6, 12, 18 and 24 months, and professional maintenance every 3 months. **Results**: 102 subjects were enrolled (test, n=48; control, n=54). The control group showed loss of clinical attachment (CA) around treated implants over the course of the study ($p<0.05$), while the test group was stable for this parameter. The difference between groups (0.55 mm) for CA change between baseline and 24 months (primary outcome variable) was statistically significant ($p<0.05$). Red complex pathogens were only reduced in the test group at 24 months. The implants with no history of peri-implantitis had a significant reduction in the percentage of sites with bleeding on probing and in mean probing depth in the test group, throughout the study ($p<0.05$). This improvement was not observed in the control group. **Conclusion**: A toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining a healthy peri-implant environment around treated implants and around implants with no history of peri-implantitis during a 2-year maintenance program.

Key-words: Peri-implantitis; Triclosan; Toothpaste; Therapeutics; Maintenance

Introduction

Although dental implants have a high success rate, the prevalence of peri-implantitis has been rising worldwide (Zitzmann & Berglundh 2008, Mombelli et al. 2012, Derks & Tomasi 2015, Derks et al. 2016, Salvi et al. 2017). Similarly to periodontitis, peri-implantitis are complex infections caused by oral pathogens that colonize the oral cavity (Shibli et al. 2008, Heitz-Mayfield & Lang 2010). A recent systematic review suggested an association between recognized periodontal pathogens, such as *Porphyromonas gingivalis, Treponema denticola* and *Tannerella forsythia*, and peri-implantitis (Perez-Chaparro et al. 2016).

Several anti-infective treatments have been proposed to treat peri-implantitis. Although an ideal and definitive therapy has not yet been established (Heitz-Mayfield & Mombelli 2014, Shibli et al. 2015), one of the most commonly used protocols is open-flap mechanical/chemical decontamination of the implant surfaces (Duarte et al. 2009, Figuero et al. 2014). In addition, it has been well established that after the active treatment phase of peri-implantitis, it is essential that patients enter a maintenance phase, similar to that followed by patients who have had periodontitis (Heitz-Mayfield et al. 2016, Ramanauskaite & Tervonen 2016). One of the main risk indicators for peri-implantitis is poor oral hygiene (Lindhe et al. 2008), so the maintenance phase should include strict control of the supra and subgingival biofilms. Several methods, including the use of dental and interdental brushes, are usually recommended for the mechanical control of biofilm accumulated in implant surfaces; however, many patients are not able to effectively remove this biofilm (Cumming & Loe 1973, Tonetti et al. 2015). This could be due to their own inability to perform proper supragingival plaque control (Wilson 1987). Thus, the use of a chemical adjunct to traditional mechanical methods during the maintenance phase of peri-implantitis treatment could improve the long term stability of dental implants. Among the several antimicrobial agents used to control biofilm accumulation in the oral cavity, triclosan is one of the most effective due to his anti-plaque efficacy (Riley & Lamont 2013). It has broad antimicrobial spectrum, with activity against Gram-positive, Gram-negative bacteria and fungi (Fine et al. 1998, Xu et al. 2005, Haraszthy et al. 2010). In addition, triclosan has an anti-inflammatory effect (Gaffar et al. 1995, Modeer et al.

1996, Panagakos et al. 2005). Two previous studies, both with 6-months of follow-up, have shown beneficial effects with the use of triclosan-containing toothpastes compared to control toothpastes, in patients presenting implants with no history of peri-implantitis (Sreenivasan et al. 2011) or patients with mucositis (Ramberg et al. 2009). However, no studies to date have evaluated the effects of toothpastes containing triclosan or other antimicrobials in the maintenance phase of individuals treated for peri-implantitis.

Therefore, the aim of this study was to evaluate the clinical and microbiological effects of a toothpaste containing 0.3% triclosan on implants treated for peri-implantitis and enrolled in a regular maintenance program. A secondary aim was to evaluate the effects of the toothpaste on the implants with no history of peri-implantitis in these patients.

Material and Methods

Sample size calculation

This study was designed to compare the effects of two different toothpastes, with and without triclosan, in the stability of tissues around implants that have been treated for peri-implantitis. The ideal sample size to assure adequate power for this randomized clinical trial (RCT) was calculated considering differences of at least 0.5 mm in clinical attachment (CA) change between groups and assuming a standard deviation of 0.8 (Mendonça et al. 2009). Based on these calculations, it was defined that 41 subjects per group would be necessary to provide an 80% power with an α of 0.05. Considering an attrition of about 25%, it was established that at least 53 subjects should be included in each treatment group.

Subject population and inclusion/exclusion criteria

Study participants were selected from the population referred to the Center for Clinical Trials of Guarulhos University (Guarulhos, SP, Brazil) and the Diagnostic Clinic of State University of Maringa (Maringa, PR, Brazil). Subjects that met the study inclusion and exclusion criteria were invited to participate into the study. Detailed medical, periodontal and dental/implant histories were obtained. All eligible subjects were informed of the nature, potential risks and benefits of their participation

in the study and signed a Term of Informed Consent. The Clinical Research Ethics Committee of Guarulhos University and State University of Maringa approved the study protocol (CAAE – 0007.0.132.000-10 and 205/2010 - 049/2013, respectively).

The inclusion criteria were as follows: males and females aged 18 to 70 years-old, in general good health, with a minimum of 1 dental implant in function for at least one year with untreated peri-implantitis defined as: probing depth (PD) ≥ 5 mm, bleeding on probing (BOP) and/or suppuration, radiographic bone loss involving 3 mm from the implant shoulder to the first visible bone-to-implant contact (Shibli et al. 2008). The exclusion criteria were as follows: subjects with ≥ 6 sites with PD ≥ 5 mm or individuals that received periodontal treatment within three months prior to entering the study, inability to perform proper supragingival plaque control (e.g. due to improper restoration design or lack of skills), poorly-adapted implant supported restoration, diabetes, pregnancy, nursing, history of allergies to triclosan, fluoride or any other ingredient of oral care products, alcohol or drug abuse, any systemic diseases that could affect post-operative healing or that required antibiotic premedication for routine dental therapy, long-term use of mouthrinses, anti-inflammatory medications or any other drug that could interfere with the study outcomes within three months prior to entering the study, antibiotics use within six months prior to entering the study and participation in any other clinical study within three months prior to entering the study.

Experimental design and treatment protocol

This Phase III, randomized, parallel, double blinded, two-center clinical study was designed in two phases, a surgical and a maintenance phase. Before the study started, the two coordinators (M.Fe. and M.A.) used a computer program (www.sealedenvelope.com) to randomly allocate subjects (1:1 allocation ratio in blocks of four) into two groups of subjects that should brush twice a day with a toothpaste containing (i) 0.3% triclosan, 2.0% Gantrez copolymer and 1450 ppm fluoride (Test Group) or (ii) 1450 ppm fluoride (Control Group).

At the beginning of the study, all subjects received oral hygiene instructions (OHI), full-mouth supragingival plaque removal and prophylaxis. Subgingival scaling was administered to all sites exhibiting PD ≥ 4 mm. Partial and total fixed

suprastructures on implants were removed before treatment. Subjects were given a soft bristle adult toothbrush, dental floss, and interdental toothbrushes, according to their individual needs. Subsequently, the implants with peri-implantitis received anti-infectious treatment (Treated Implants) as follows: after local anesthesia (2% lidocaine with 1:100,000 epinephrine), intrasulcular incisions were done in order to create a horizontal flap extending beyond the adjacent teeth and/or implants. Buccal and lingual full-thickness flaps were dissected, and granulation tissue was removed to expose the implant threads and bone defect. To remove biofilm and calculus, the implant surface was scaled with teflon curettes and decontaminated with bicarbonate jet (Jet Sonic System). The flap was repositioned in its original position and stabilized with interrupted sutures, which were removed after 10 days. Analgesics were prescribed to all subjects and they were instructed to rinse with a 0.12% chlorhexidine mouthwash twice a day for 7 days.

Subjects returned to the clinic 60 days after the surgeries for clinical and microbiological monitoring (baseline) and to receive the toothpaste according to their experimental group (Test or Control). They received a regular adult soft bristles toothbrush (Colgate Palmolive, Brazil) as well as dental floss (Colgate Palmolive, Brazil) and interdental toothbrushes (Colgate Palmolive, Brazil), according to their individual needs. They also received information about the importance of keeping an excellent oral hygiene over the course of the study and were instructed to brush their teeth for one minute twice a day (morning and evening) using only the toothbrush and toothpaste provided. There were no specific instructions related to dietary habits or smoking. All subjects returned for maintenance visits every 3 months and received OHI, supragingival and subgingival biofilm removal from teeth and implants, and oral prophylaxis. The products (toothbrushes and toothpastes) were replaced at all maintenance visits.

Colgate Palmolive (São Paulo, Brazil) prepared the Test and Control toothpastes and placed them in opaque identical tubes labeled-coded for each group (F or P, respectively). At each site, the study coordinators (M.Fe. and M.A.) received the toothpastes/toothbrushes and placed them in indistinguishable plastic bags numbered from 1 to 53 according to the randomization list, which was also labeled-

coded. This process was done to ensure allocation concealment. All study personnel were blinded as to products allocation. Code breaking was done after data analysis.

Monitoring of compliance and adverse events

At each maintenance visit the subjects were asked to return the used toothbrushes and the toothpaste tubes in order to monitoring compliance. In order to checked for remaining paste and the condition of the toothbrushes were also evaluated. The examiners asked the subjects if they had experienced any undesirable effect that could be associated with the use of the toothpastes. If any adverse events were observed, the subject should be instructed to discontinue the toothpaste and withdrawn from the study.

Clinical monitoring

Three calibrated examiners, two from Guarulhos University (T.O and R.M.) and one from the State University of Maringa (F.M.) performed all clinical examinations. The following parameters were recorded at 6 sites per implants excluding third molars, using a North Carolina periodontal probe (Hu-Friedy, Chicago, IL, USA): Plaque Index (PI) (Turesky et al. 1970, Quigley & Hein 1962) (The plaque was disclosed using a disclosing solution and recorded as follows: score 0 = absence of plaque; score 1 = separate flecks of plaque on the cervical margin; score 2 = a thin, continuous band of plaque [up to 1mm] at the cervical margin of the tooth; score 3 = a band of plaque wider than 1mm, but covering less than 1/3 of the tooth crown; score 4 = plaque covering at least 1/3, but less than 2/3 of the crown of the tooth; score 5 = plaque covering 2/3-crown or more of the crown of the tooth), Gingival Index (GI) (Loe & Silness 1963) (score 0 = absence of inflammation; score 1 = mild inflammation – slightly slight change in color and little change in texture; score 2 = moderate inflammation – moderate glazing, redness, edema and hypertrophy; score 3 = severe inflammation - marked redness and hypertrophy. Tendency to spontaneous bleeding), presence or absence of BOP and suppuration, PD (mm) and relative clinical attachment level (CAL) (distance in mm from the cement-enamel junction/implant shoulder to the most apical portion of the sulcus or periodontal/peri-implant pocket). Implant-supported restorations retained by screws were removed for clinical records; cement retained restoration were not removed. The clinical monitoring was performed at baseline, 3, 6, 12, 18 and 24 months.

Microbiological monitoring

After supragingival plaque removal, one subgingival biofilm sample from the deepest site (pre-baseline) of each implant treated for peri-implantitis was collected with individual sterile mini-Gracey curettes (#11–12). The samples were immediately placed in separate Eppendorf tubes containing 0.15 ml of TE (10 mM Tris-HCl, 1 mM EDTA, pH 7.6). One hundred microlitres of 0.5 M NaOH was added to each tube and the samples were dispersed using a vortex mixer. Counts of 40 bacterial species were determined in each sample, using the checkerboard DNA–DNA hybridization technique (Socransky et al. 1994, Mestnik et al. 2010) at the Laboratory of Microbiology of Guarulhos University. Microbiological monitoring was performed at baseline, 3, 6, 12, 18 and 24 months.

Radiographic monitoring

Standardized intra-oral periapical radiographs were obtained using a dental X-ray machine equipped with a 35-cm-long cone (Dabiatlante, Ribeirão Preto, SP, Brazil). Exposure parameters were 70 kV (peak), 15mA and 1/4 s at a focus-to-sensor distance of 30 cm. The radiographs were captured with a digital camera and transferred to a personal computer. Image processing software was used to store the digitized images. Subsequently, the images were displayed on a monitor, linear measurements were taken with a software (Image Pro-Plus 4.5, Media Cybernetics Inc., Silver Spring, MD, USA) and measurements of the peri-implant bone loss were taken. Measurements were performed from the implant shoulder to the first visible bone-to-implant contact. Radiographic monitoring was performed at baseline, 3, 6, 12, 18 and 24 months.

Termination criteria

It was determined that any implant showing ≥ 2 mm of bone loss between two appointments should be withdrawn from the study to receive additional treatment, and those showing mobility should be removed.

Calibration exercise

The calibration exercise was conducted before the beginning of the study and annually for the duration of the study, according to the methodology proposed by Araujo et al. (2003). The Standard Error of the Mean (S.E.M) and the Mean Percentage Error (M.P.E) for the continuous clinical parameters (PD, CAL) were evaluated in five individuals presenting implants and not participating in the study. The S.E.M and M.P.E intra-examiner were respectively 0.2 mm and 5.6% for PD; 0.33 mm and 8.6% for CAL, and 0.18mm and 2.9% for vertical bone loss. For the categorical variables (PI, GI, BOP and suppuration), considering the presence or absence of the clinical parameter, the mean of the level of agreement for the examiner was obtained, obtaining a concordance above 93% (Kappa test).

Primary outcome variable and statistical analysis

The primary outcome variable was the difference among groups for the change in CA from baseline to 24 months. Each individual clinical parameter was computed for each subject, and averaged across subjects in each group separately. The significance of differences between the two groups at baseline for the mean age of the population, mean number per subject of treated implants and implants with no history of peri-implantitis, PI, GI, percentage of sites with BOP, mean PD and mean CAL for all implants was sought using Student T-test. The Fisher's exact test was used to compare the differences in the frequency of gender.

The significance of differences within each group over time was assessed by repeated measures ANOVA and Tukey's multiple comparison tests. The significance of differences between the two treatment groups at each time point was assessed by ANCOVA adjusted for baseline values and treatment center. Differences between the two treatment groups in proportions of the microbial complexes were sought using ANCOVA adjusted for baseline mean values of each microbial complex and study center. The data were evaluated using intention-to-treat analysis with last observation carried forward. The level of significance was set at a p-value of 0.05.

Results

Subject retention, adverse effects and compliance

The study was conducted between June 2010 and December 2014. Figure 1 presents the flow diagram of the study design. Two thousand five hundred subjects were assessed for eligibility and 109 entered the study at the Pre-baseline phase and received surgeries: Test Group (n=53 subjects/142 treated implants); Control Group (n=56 subjects/145 treated implants). All evaluated implants presented rough surfaces. After surgery, 48 subjects/131 treated implants in the Test Group and 54 subjects/142 treated implants in the Control group entered the Experimental phase. Six subjects/13 treated implants (1 lost implant due to mobility) and 5 subjects/10 treated implants (2 lost implants due to mobility) were lost over the course of the study in the Test and Control groups, respectively. Forty-two subjects/118 treated implants and 49 subjects/132 treated implants in the Test and Control groups, respectively completed the study up to 24 months. No adverse events were reported and lack of compliance was not detected. All subjects returned the used and unused study products at the maintenance visits.

Clinical findings

Table 1 presents clinical and demographic data of the population evaluated and data related to the implants studied. No statistically significant differences were observed between the two groups at baseline. In addition, PI, GI, percentage of sites with BOP, mean PD and mean CAL of treated implants or implants with no history of peri-implantitis did not differ between the two groups at baseline (data not shown).

Table 2 presents the clinical parameters between the pre-baseline and baseline time points (i.e. results of treatment of peri-implantitis), in both groups. The average PD and CAL around the implants (for all sites and for those with ≥ 5 mm) were statistically significantly reduced after treatment. In addition, the percentage of sites presenting BOP showed a significant reduction from pre-baseline to baseline in both groups.

Figures 2.a and 2.b present the comparisons between the two groups for the changes occurring in CA, PD, BOP, PI and GI between baseline and each follow-up time point for treated implants or implants with no history of peri-implantitis, and

Table 3 shows the mean values of these clinical parameters at all time points. The control group, for treated implants, showed loss of attachment over the course of the study ($p<0.05$) while those in the test group were stable for this parameter (Table 3 and Figure 2a). The difference between groups for CA change between baseline and 24 months (0.55 mm) for treated implants was statistically significant (primary outcome variable, Figure 2.a). Both groups showed a statistically significant reduction in mean PD and GI and the Control group an increase in PI, for treated implants over the course of the study (Figures 2.a, 2.b, Table 3). The test group, for implants with no history of peri-implantitis, showed a significant reduction in the percentage of sites with BOP and in mean PD throughout the study ($p<0.05$). This benefit was not observed in the control group (Table 3).

Figure 3 shows the mean values and mean changes occurring in bone height throughout the study. The treated implants at the control group, exhibited significant bone loss after the 12 months time-point ($p<0.05$). The mean percentages of sites gaining or loosing ≥ 2 mm of CA during the study period are described in Table 4. The test group had a higher mean percentage of sites around treated implants that gained attachment between baseline-18 and baseline-24 months, as well as fewer sites that lost CA between baseline-6 months, in comparison with the control group ($p<0.05$). Although no statistically significant differences were observed between the two toothpaste groups for the implants with no history of peri-implantitis, the control group had an increase in the mean percentage of sites loosing ≥ 2 mm of CA from baseline-3 months to baseline-24 months ($p<0.05$).

Table 5 presents the effects of both treatments in the percentage of residual sites around treated implants. The mean percentage of sites with PD ≥ 5mm were reduced in both groups over the course of the study, but only the test group exhibited a statistically significant reduction in the mean number of sites with PD ≥ 6mm and PD ≥ 7mm ($p<0.05$) (Table 5).

The mean proportions of the microbial complexes are represented in Figure 4. The proportions of the red complex pathogens, *P. gingivalis*, *T. denticola* and *T. forsythia* decreased significantly from baseline to 24 months in the test group, for treated implants (Figure 4).

DISCUSSION

The data of this RCT showed that a toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining the peri-implant tissue stability of implants treated for peri-implantitis and were enrolled in a regular professional maintenance program. In addition, toothpaste containing 0.3% triclosan also led to a reduction in BOP and PD around implants with no history of peri-implantitis.

After 24 months, the group that brushed with the triclosan toothpaste showed CA stability around treated implants, while the control group lost attachment. The difference between groups for CA change from baseline to 24 months was 0.55 mm ($p<0.05$) (primary outcome, Figure 2a), meaning that the toothpaste containing 0.3% triclosan was 47% more effective than the control dentifrice in maintaining the clinical stability around treated implants. In addition, the mean percentage of sites gaining ≥ 2 mm of CA at 24 months around treated implants was higher in the test group than in the control group ($p<0.05$). The test group also showed stability of the bone height, while the control group exhibited bone loss over the course of the study. Interestingly, the toothpaste containing triclosan also benefited the implants with no history of peri-implantitis by reducing mean PD and the mean percentage of sites with BOP around these implants, over the course of the study.

In agreement with the clinical features, the microbiological data showed that the toothpaste containing 0.3% triclosan yielded a beneficial change in the subgingival biofilm composition around treated implants. The proportions of the pathogens from the red complex did not change from baseline to 24 months in the control group (~9%), while a statistically significant reduction in this complex, from 9.4% at baseline to 6.4% at 24 months, was observed in the test group. This is considered an important beneficial effect of the triclosan toothpaste, as previous studies evaluating different periodontal treatments suggested that residual proportions of red complex close to 10% are associated with clinical instability (Feres et al. 2015). Sreenivasan et al. (2011) studied a population presenting at least one implant without peri-implantitis. Volunteers were randomly assigned to brush for 6 months with toothpastes containing or not triclosan. In accordance to our data, they observed that the triclosan toothpaste was more effective than the control in reducing the levels of several oral microorganisms including a few periodontal pathogens,

such as *Aggregatibacter actinomycetemcomitans, Campylobacter rectus*, *Prevotella melaninogenica*, *T. forsythia* and *P. gingivalis*. The toothpaste containing triclosan was also more effective than the control in reducing PI, GI and BOP on the implants.

No studies to date have reported the effects of toothpastes containing triclosan or other antimicrobial agents in the maintenance phase of peri-implantitis treatment. Nonetheless, Ramberg et al. (2009) evaluated the effects of a toothpaste containing triclosan on implants showing signs of mucositis in a population that had been treated for periodontitis. The authors observed that subjects who during a 6-month period regularly brushed with the triclosan containing toothpaste, exhibited greater reductions in implants PD and BOP than those who brushed with a regular fluoride toothpaste. Similarly to those findings, in our study the implants without peri-implantitis in the triclosan group also showed a significant improvement in these two parameters over the course of the study, but only after 1 year of brushing.

Interestingly, triclosan delivered supragingivally was able to yield clinically relevant benefits on subgingival parameters, including the subgingival microbial profile. Feres et al. (2009) reported this same kind of effect for chlorhexidine (CHX) mouthrinse, in periodontal parameters. Subjects with periodontitis who rinsed twice a day with CHX for 2 months had lower proportions of red complex species and better clinical outcomes at 4 months after the withdraw of the agent. The subgingival benefits observed with CHX rinsing in that study as well with the triclosan toothpaste in the present investigation might be attributed to the effects of these agents in controlling pathogens that might be present in different oral surfaces and could colonize the recently scaled pockets around teeth (Feres et al. 2009) and probably around implants. Another possible effect is the reduction of plaque/inflammation, which can prevent the availability of nutrients necessary for periodontal pathogens multiplication (Socransky & Haffajee 2002). In this regard, triclosan has shown to have good antimicrobial (Fine et al. 1998, Xu et al. 2005, Haraszthy et al. 2010) and anti-inflammatory effects (Gaffar et al. 1995, Modeer et al. 1996, Panagakos et al. 2005) and is normally associated with low incidence of side-effects (Riley & Lamont 2013). In addition, its delivery to the oral cavity in toothpastes has the advantage of not requiring changes in patient's habits, assuring a high degree of compliance. Another important point of consideration is that the participants of this study were enrolled in a regular maintenance program that included supragingival and

subgingival plaque removal and OHI every three months. Thus, the triclosan toothpaste was able to yield these important clinical and microbiological benefits even in this well-controlled population.

The main strength of this study was to be the first double blind, placebo controlled RCT to report the effects of an adjunctive antimicrobial agent in the maintenance phase of peri-implantitis treatment. Other strengths of this study were: the number of patients/implants included and the follow-up period of 24 months. The results have direct clinical applicability, as they might benefit patients in the daily clinical practice. One limitation of this study was the Index used to evaluate plaque accumulation (Turesky et al. 1970, Quigley & Hein 1962). Although quite effective for natural teeth, this index has some limitations for implants and implants-supported restoration, due to difficulties with the dying step. Implant-supported resin restorations might be permanently stained. In addition, implant-supported restorations made of ceramic normally accumulate less plaque. As a consequence, PI in the implant surfaces was considerably low since the baseline assessment. A dichotomous parameter would be more appropriate for measuring plaque accumulation in dental implants.

In conclusion, the data of the present study showed that a toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining peri-implant clinical stability and a more beneficial microbial profile around implants treated for peri-implantitis in subjects who were enrolled in a regular maintenance program for 2 years. In addition, the test toothpaste led to additional clinical benefits around implants with no history of peri-implantitis.

Acknowledgments

This study was supported by Colgate-Palmolive, Technology Center, (Piscataway, New Jersey, USA) and Latin America Oral Health Association (LAOHA).

REFERENCES

Araujo, M. W., Hovey, K. M., Benedek, J. R., Grossi, S. G., Dorn, J., Wactawski-Wende, J., Genco, R. J. & Trevisan, M. (2003) Reproducibility of probing depth measurement using a constant-force electronic probe: analysis of inter- and intraexaminer variability. *Journal of Periodontology* **74**, 1736-1740.

Cumming, B. R. & Loe, H. (1973) Consistency of plaque distribution in individuals without special home care instruction. *Journal of Periodontal Research* **8**, 94-100.

de Mendonça, A. C., Santos, V. R., Cesar-Neto, J. B. & Duarte, P. M. (2009) Tumor necrosis factor-alpha levels after surgical anti-infective mechanical therapy for peri-implantitis: a 12-month follow-up. *Journal of Periodontology* **80**, 693-699.

Derks, J., Schaller, D., Hakansson, J., Wennstrom, J. L., Tomasi, C. & Berglundh, T. (2016) Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-implantitis. *Journal of Dental Research* **95**, 43-49.

Derks, J. & Tomasi, C. (2015) Peri-implant health and disease. A systematic review of current epidemiology. *Journal of Clinical Periodontology* **42 Suppl 16**, S158-171.

Duarte, P. M., de Mendonça, A. C., Maximo, M. B., Santos, V. R., Bastos, M. F. & Nociti, F. H. (2009) Effect of anti-infective mechanical therapy on clinical parameters and cytokine levels in human peri-implant diseases. *Journal of Periodontology* **80**, 234-243.

Feres, M., Figueiredo, L. C., Soares, G. M. & Faveri, M. (2015) Systemic antibiotics in the treatment of periodontitis. *Periodontology 2000* **67**, 131-186.

Feres, M., Gursky, L.C., Faveri, M., Tsuzuki, C.O., Figueiredo, L.C. (2009) Clinical and microbiological benefits of strict supragingival plaque control as part of the active phase of periodontal therapy. *Journal of Clinical Periodontology* **36(10)**:857-867.

Figuero, E., Graziani, F., Sanz, I., Herrera, D. & Sanz, M. (2014) Management of peri-implant mucositis and peri-implantitis. *Periodontology 2000* **66**, 255-273.

Fine, D. H., Furgang, D., Bonta, Y., DeVizio, W., Volpe, A. R., Reynolds, H., Zambon, J. J. & Dunford, R. G. (1998) Efficacy of a triclosan/NaF dentifrice in the control of plaque and gingivitis and concurrent oral microflora monitoring. *American Journal of Dentistry* **11**, 259-270.

Gaffar, A., Scherl, D., Afflitto, J. & Coleman, E. J. (1995) The effect of triclosan on mediators of gingival inflammation. *Journal of Clinical Periodontology* **22**, 480-484.

Haraszthy, V. I., Zambon, J. J. & Sreenivasan, P. K. (2010) Evaluation of the antimicrobial activity of dentifrices on human oral bacteria. *The Journal of Clinical Dentistry* **21**, 96-100.

Heitz-Mayfield, L. J. & Lang, N. P. (2010) Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis. *Periodontology 2000* **53**, 167-181.

Heitz-Mayfield, L. J. & Mombelli, A. (2014) The therapy of peri-implantitis: a systematic review. *The International Journal of Oral & Maxillofacial Implants* **29 Suppl**, 325-345.

Heitz-Mayfield, L. J., Salvi, G. E., Mombelli, A., Faddy, M., Lang, N. P. & Implant Complication Research, G. (2012) Anti-infective surgical therapy of peri-implantitis. A 12-month prospective clinical study. *Clinical Oral Implants Research* **23**, 205-210.

Heitz-Mayfield, L. J., Salvi, G. E., Mombelli, A., Loup, P. J., Heitz, F., Kruger, E. & Lang, N. P. (2016) Supportive peri-implant therapy following anti-infective surgical peri-implantitis treatment: 5-year survival and success. *Clinical Oral Implants Research* doi:10.1111/clr.12910.

Lindhe, J., Meyle, J. & Group, D. o. E. W. o. P. (2008) Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. *Journal of Clinical Periodontology* **35**, 282-285.

Loe, H. & Silness, J. (1963) Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontologica Scandinavica* **21**, 533-551.

Mestnik, M. J., Feres, M., Figueiredo, L. C., Duarte, P. M., Lira, E. A. & Faveri, M. (2010) Short-term benefits of the adjunctive use of metronidazole plus amoxicillin in the microbial profile and in the clinical parameters of subjects with generalized aggressive periodontitis. *Journal of Clinical Periodontology* **37**, 353-365.

Modeer, T., Bengtsson, A. & Rolla, G. (1996) Triclosan reduces prostaglandin biosynthesis in human gingival fibroblasts challenged with interleukin-1 in vitro. *Journal of Clinical Periodontology* **23**, 927-933.

Mombelli, A., Muller, N. & Cionca, N. (2012) The epidemiology of peri-implantitis. *Clinical Oral Implants Research* **23 Suppl 6**, 67-76.

Panagakos, F. S., Volpe, A. R., Petrone, M. E., DeVizio, W., Davies, R. M. & Proskin, H. M. (2005) Advanced oral antibacterial/anti-inflammatory technology: A comprehensive review of the clinical benefits of a triclosan/copolymer/fluoride dentifrice. *The Journal of Clinical Dentistry* **16 Suppl**, S1-19.

Perez-Chaparro, P. J., Duarte, P. M., Shibli, J. A., Montenegro, S., Lacerda Heluy, S., Figueiredo, L. C., Faveri, M. & Feres, M. (2016) The Current Weight of Evidence of the Microbiologic Profile Associated With Peri-Implantitis: A Systematic Review. *Journal of Periodontology* **87**, 1295-1304.

Quigley, G. A. & Hein, J. W. (1962) Comparative cleansing efficiency of manual and power brushing. *Journal of American Dental Association* **65**, 26–29.

Ramanauskaite, A. & Tervonen, T. (2016) The Efficacy of Supportive Peri-Implant Therapies in Preventing Peri-Implantitis and Implant Loss: a Systematic Review of the Literature. *Journal of Oral & Maxillofacial Research* **7**, e12.

Ramberg, P., Lindhe, J., Botticelli, D. & Botticelli, A. (2009) The effect of a triclosan dentifrice on mucositis in subjects with dental implants: a six-month clinical study. *The Journal of Clinical Dentistry* **20**, 103-107.

Riley, P. & Lamont, T. (2013) Triclosan/copolymer containing toothpastes for oral health. *Cochrane Database Syst Rev***,** CD010514. doi:10.1002/14651858.CD010514.pub2.

Salvi, G. E., Cosgarea, R. & Sculean, A. (2017) Prevalence and Mechanisms of Peri-implant Diseases. *Journal of Dental Research* **96**, 31-37.

Shibli, J., Ivanovski, S., Park, Y.B., Alarcon, M., Cheung, K.M., Duncan, W., Ettiene, D., Girl, D., Halhal, R., Kakar, M., Kim, S.T., Kim, T.S., Matheos, N., Narongsak, L., Ouyahoun, J.P., Panikar, A., Shin, S.I., Wagh, A., Won, J.U. (2015) Group D. Consensus report. Implants--peri-implant (hard and soft tissue) interactions in health and disease: the impact of explosion of implant manufacturers. *Journal of the International Academy of Periodontology* **17**, 71-73.

Shibli, J.A., Melo, L., Ferrari, D.S., Figueiredo, L.C., Faveri, M. & Feres, M. (2008) Composition of supra- and subgingival biofilm of subjects with healthy and diseased implants. *Clinical Oral Implants Research* **19**, 975-982.

Socransky, S.S. & Haffajee, A.D. (2002) Dental biofilms: difficult therapeutic targets. Periodontology 2000 **28**:12-55.

Socransky, S. S., Smith, C., Martin, L., Paster, B. J., Dewhirst, F. E. & Levin, A. E. (1994) "Checkerboard" DNA-DNA hybridization. *Biotechniques* **17**, 788-792.

Sreenivasan, P. K., Vered, Y., Zini, A., Mann, J., Kolog, H., Steinberg, D., Zambon, J. J., Haraszthy, V. I., da Silva, M. P. & De Vizio, W. (2011) A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. *Journal of Clinical Periodontology* **38**, 33-42.

Tonetti, M. S., Eickholz, P., Loos, B. G., Papapanou, P., van der Velden, U., Armitage, G., Bouchard, P., Deinzer, R., Dietrich, T., Hughes, F., Kocher, T., Lang, N. P., Lopez, R., Needleman, I., Newton, T., Nibali, L., Pretzl, B., Ramseier, C., Sanz-Sanchez, I., Schlagenhauf, U. & Suvan, J. E. (2015) Principles in prevention of periodontal diseases: Consensus report of group 1 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. *Journal of Clinical Periodontology* **42 Suppl 16**, S5-11.

Turesky, S., Gilmore, N.D. & Glickman, I. (1970) Reduced plaque formation by the chloromethyl analogue of victamine C. *Journal of Periodontology* **41**, 41–43.

Wilson, T.G. Jr. (1987) Compliance. A review of the literature with possible applications to periodontics. *Journal of Periodontology* **58**, 706-714.

Xu, T., Deshmukh, M., Barnes, V. M., Trivedi, H. M., Du-Thumm, L., Richter, R. & Cummins, D. (2005) Analysis of the antibacterial activity and plaque control benefit of colgate total dentifrice via clinical evaluation and real-time polymerase chain reaction. *The Journal of Clinical Dentistry* **16**, 117-122.

Zitzmann, N. U. & Berglundh, T. (2008) Definition and prevalence of peri-implant diseases. *Journal of Clinical Periodontology* **35**, 286-291.

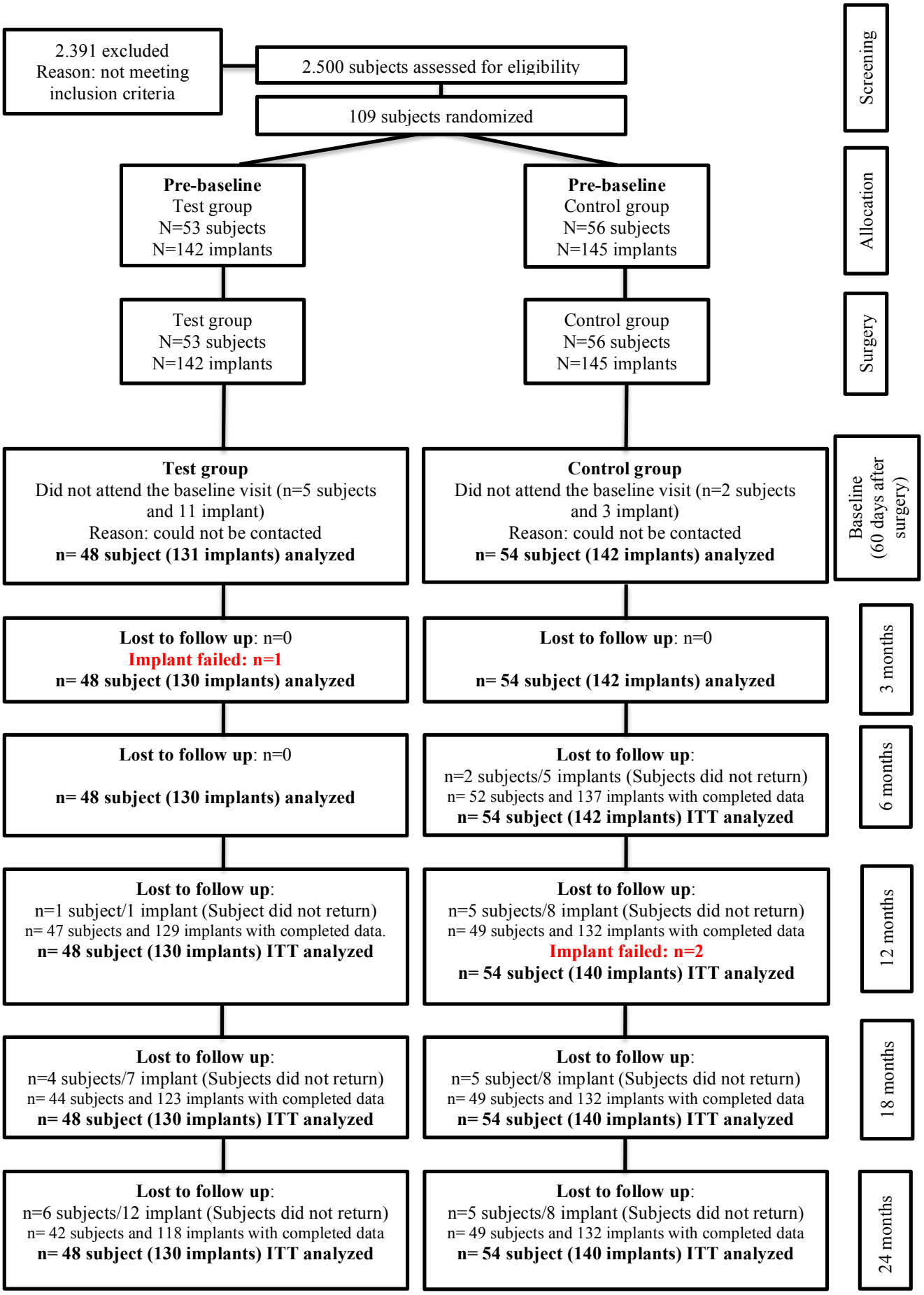


Figure 1. Study Flow Chart

Table 1. Baseline data and demographic characteristics of the population studied, stratified per group.

Variables	Groups		p-value
	Test	Control	
Treated implants			
Subjects (n)	48	54	
Age (mean ± SD)	52.83 ± 8.90	54.74 ± 9.18	0.291
Gender (% Female)	75	57	0.063
Smokers	8	5	0.374
Implants (total n)	131	142	
Implants *per* subject (mean ± SD)	2.73 ± 2.03	2.61 ± 1.85	0.759
Time of loading (years)	5.51 ± 2.48	4.89 ± 3.0 3	0.1369
Cemented / screw-retained (%)	16.5% / 83.5%	18.6% / 81.4%	0.8457
Implant location (%) Anterior / Posterior	33.0% / 67.0%	25.5% / 74.5%	0.3304
Type of restoration (%) Single FPD Overdenture	 30.2% 30.2% 8.7%	 38.5% 56.0% 5.5%	0.3841
Implants with no history of peri-implantitis			
Subjects (n)	30	31	
Healthy implants (total n)	119	116	
Healthy implants *per* subject (mean ± SD)	3.91 ± 1.21	3.62 ± 1.42	0.875

The significance of differences between the two groups at baseline for the mean age of the population, smokers, mean number per subject of implants treated and implants with no history of peri-implantitis was sought using Student T-test. The Fisher's exact test was used to compare the differences in the frequency of gender. n= number; SD: standard deviation; %: percentage.

Table 2. Mean clinical parameters at Pre-baseline and at Baseline, and mean changes in these parameters between the two time-points.

Variables	Time	Groups		p-value
		Test	Control	
Plaque Index	Pre-baseline	0.51 ± 1.11	0.32 ± 0.79	0.312
	Baseline	0.48 ± 0.87	0.29 ± 0.64	0.226
	Δ	0.03 ± 0.83	0.02 ± 0.84	0.990
Gingival Index	Pre-baseline	1.31 ± 1.00	1.40 ± 1.00	0.659
	Baseline	0.89 ± 0.93	0.94 ± 0.96	0.799
	Δ	0.42 ± 0.83	0.46 ± 0.98	0.825
Bleeding on Probing (%)	Pre-baseline	88.0 ± 20.0[a]	86.0 ± 24.0 [a]	0.550
	Baseline	30.0 ± 34.0 [b]	33.0 ± 31.0 [b]	0.655
	Δ	58.0 ± 48.0	53.0 ± 40.0	0.523
Probing Depth (PD)	Pre-baseline	4.27 ± 0.95 [a]	4.33 ± 1.02 [a]	0.738
	Baseline	3.37 ± 0.99 [b]	3.42 ± 0.96 [b]	0.819
	Δ	0.89 ± 1.01	0.91 ± 0.99	0.914
Clinical Attachment Level (CAL)	Pre-baseline	4.56 ± 0.92 [a]	4.56 ± 0.99 [a]	0.990
	Baseline	4.31 ± 1.01 [b]	4.05 ± 0.96 [b]	0.188
	Δ	0.25 ± 1.03	0.51 ± 0.95	0.190
Sites with PD ≥5 mm				
Probing Depth (PD)	Pre-baseline	5.58 ± 0.66 [a]	5.63 ± 0.65 [a]	0.744
	Baseline	3.67 ± 1.19 [b]	3.89 ± 1.18 [b]	0.355
	Δ	1.91 ± 1.04	1.72 ± 1.13	0.405
Clinical Attachment Level (CAL)	Pre-baseline	5.73 ± 0.80 [a]	5.66 ± 0.69 [a]	0.643
	Baseline	4.52 ± 1.17 [b]	4.49 ± 1.09 [b]	0.888
	Δ	1.21 ± 0.97	1.17 ± 1.15	0.861

The significance of differences between the two groups at each time point was sought using Student T-test. n= number; SD: standard deviation; %: percentage.

Table 3. Mean (± SEM) values for clinical parameters over the course of the study.

Variable	Time-Point	Treated implants		p-value	Implants with no history of peri-implantitis		p-value
		Test	Control		Test	Control	
PI	Baseline	0.48 ± 0.87	0.29 ± 0.64 [a]		0.30 ± 0.51	0.21 ± 0.39	
	3 months	0.38 ± 0.80	0.28 ± 0.69 [a]	0.503	0.38 ± 0.85	0.21 ± 0.40	0.325
	6 months	0.31 ± 0.76	0.29 ± 0.60 [a]	0.878	0.38 ± 0.71	0.31 ± 0.51	0.661
	12 months	0.53 ± 0.99	0.29 ± 0.64 [a]	0.158	0.56 ± 0.81	0.49 ± 0.61	0.693
	18 months	0.46 ± 0.82	0.45 ± 0.79 [b]	0.990	0.58 ± 0.83	0.40 ± 0.55	0.358
	24 months	0.45 ± 0.83	0.45 ± 0.73 [b]	0.990	0.57 ± 0.80	0.50 ± 0.66	0.707
GI	Baseline	0.89 ± 0.93 [a]	0.94 ± 0.96 [a]		0.64 ± 0.93	0.62 ± 0.72	
	3 months	0.97 ± 0.94 [a]	0.85 ± 0.89 [a]	0.510	0.48 ± 0.77	0.61 ± 0.78	0.523
	6 months	0.84 ± 0.84 [a]	0.79 ± 0.89 [a]	0.754	0.36 ± 0.54	0.57 ± 0.65	0.181
	12 months	0.52 ± 0.68 [b]	0.57 ± 0.66 [b]	0.693	0.31 ± 0.49	0.36 ± 0.41	0.679
	18 months	0.48 ± 0.65 [b]	0.58 ± 0.65 [b]	0.441	0.27 ± 0.45	0.34 ± 0.45	0.560
	24 months	0.44 ± 0.65 [b]	0.52 ± 0.64 [b]	0.505	0.24 ± 0.35	0.33 ± 0.36	0.350
BOP (% of sites)	Baseline	30.0 ± 34.0 [a]	33.0 ± 31.0		39.6 ± 34.3 [a]	29.3 ± 31.7	
	3 months	26.0 ± 30.0 [a]	29.0 ± 31.0	0.669	28.2 ± 26.3	29.7 ± 29.6	0.836
	6 months	24.0 ± 28.0 [a]	34.0 ± 36.0	0.111	28.1 ± 28.4	22.2 ± 26.7	0.408
	12 months	21.8 ± 28.4 [b]	26.4 ± 33.0	0.458	29.8 ± 27.1	25.3 ± 30.0	0.544
	18 months	19.2 ± 29.4 [a]	28.7 ± 35.2	0.144	21.7 ± 24.2 [b]	22.6 ± 25.8	0.890
	24 months	22.1 ± 31.7 [a]	28.2 ± 35.1	0.645	24.1 ± 25.5 [b]	29.2 ± 30.0	0.480
PD (mm)	Baseline	3.37 ± 0.99 [a]	3.42 ± 0.96 [a]		2.86 ± 0.51 [a]	2.88 ± 0.75	
	3 months	3.22 ± 0.94 [a]	3.22 ± 1.03 [a]	0.990	2.56 ± 0.65	2.78 ± 0.71	0.202
	6 months	2.88 ± 0.92 [b]	3.05 ± 1.06 [a]	0.372	2.52 ± 0.60	2.72 ± 0.73	0.253
	12 months	2.88 ± 0.90 [b]	2.85 ± 1.15 [b]	0.892	2.36 ± 0.71 [b]	2.55 ± 0.73	0.320
	18 months	2.64 ± 0.87 [b]	2.81 ± 1.17 [b]	0.426	2.42 ± 0.63 [b]	2.53 ± 0.86	0.990
	24 months	2.74 ± 0.79 [b]	3.04 ± 1.24 [b]	0.156	2.44 ± 0.56 [b]	2.58 ± 0.90	0.829
CAL (mm)	Baseline	4.31 ± 1.01	4.05 ± 0.96 [a]		3.24 ± 0.68	3.08 ± 0.69	
	3 months	4.16 ± 1.00	4.08 ± 1.14 [a]	0.712	3.15 ± 0.73	3.18 ± 0.81	0.888
	6 months	4.09 ± 1.05	4.04 ± 1.19 [a]	0.849	3.13 ± 0.76	3.17 ± 0.82	0.828
	12 months	4.12 ± 1.14	4.01 ± 1.24 [a]	0.663	3.24 ± 1.14	3.27 ± 0.79	0.893
	18 months	3.92 ± 1.40	4.11 ± 1.38 [a]	0.486	3.27 ± 0.86	3.24 ± 0.78	0.867
	24 months	4.12 ± 1.27	4.41 ± 1.33 [b]	0.263	3.35 ± 0.82	3.32 ± 0.82	0.885

The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA, adjusted for baseline mean values and treatment center.

SEM*:* standard errors of the mean*;* PI: plaque index; GI: gingival index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment level; %: percentage; mm: millimeter.

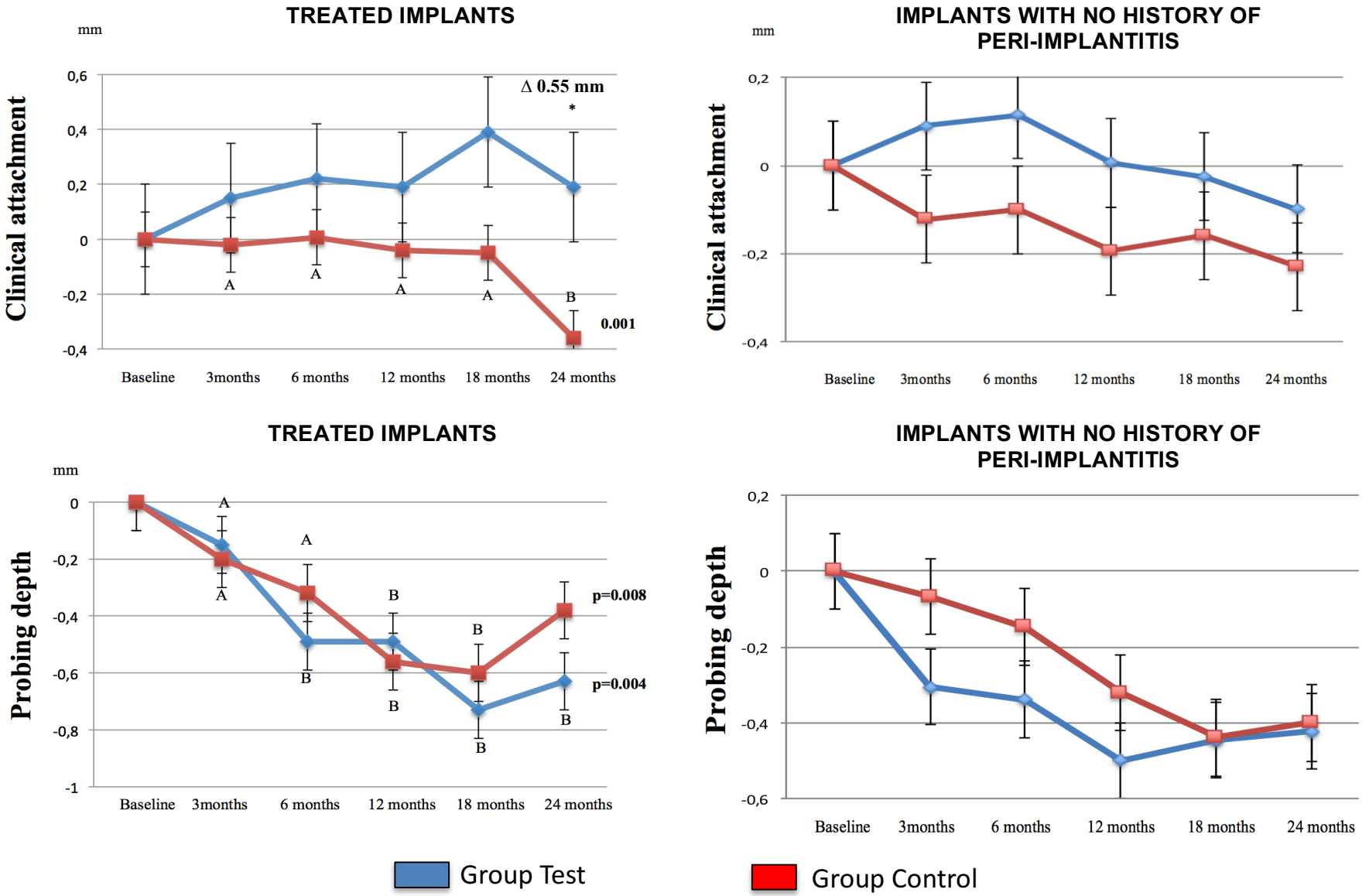


Figure 2.a Line chart of mean changes in Clinical Attachment and Probing Depth for treated implants and implants with no history of peri-implantitis between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* $p<0.05$).

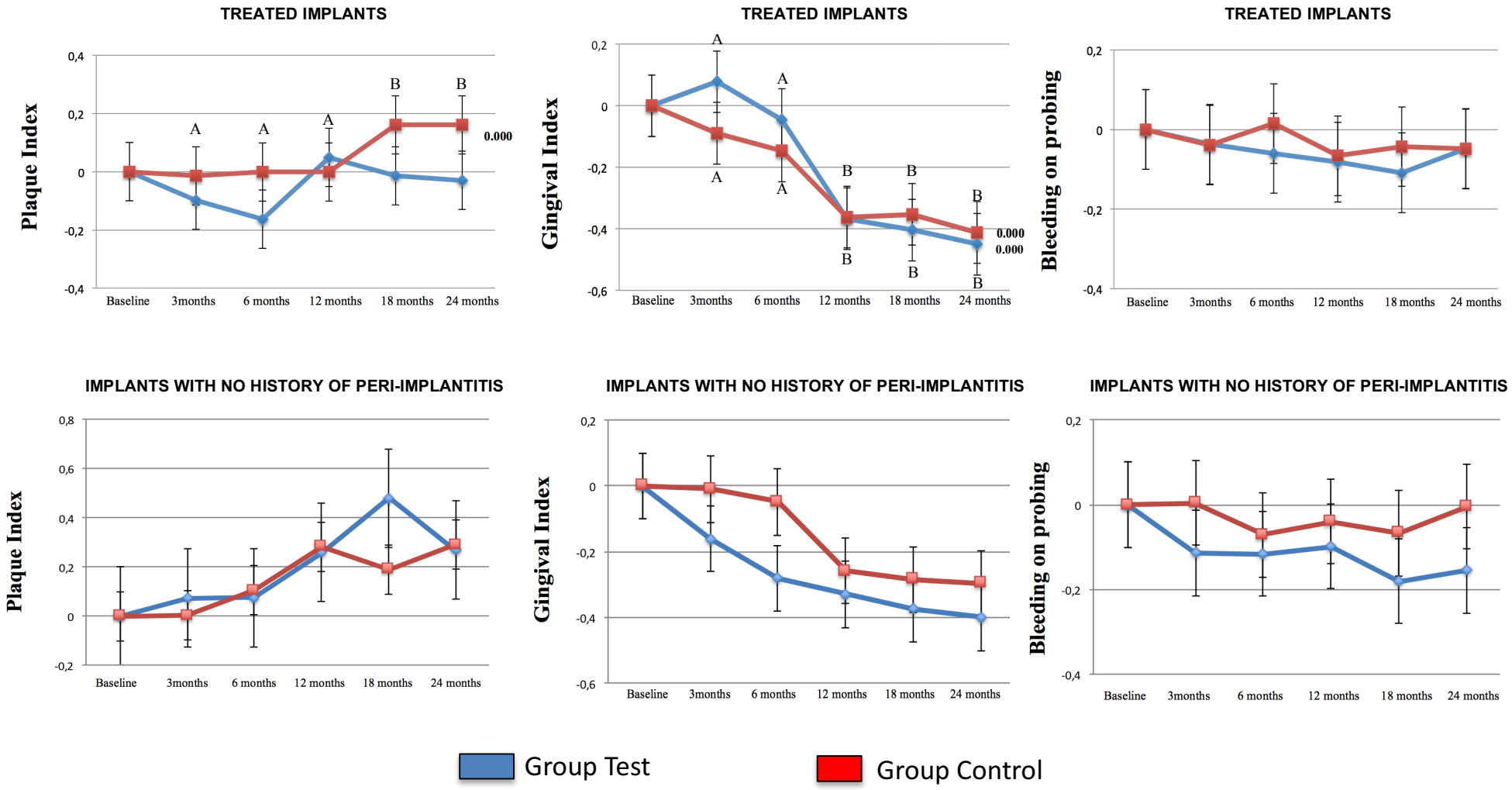


Figure 2.b Line chart of mean changes in Plaque Index, Gingival Index and Bleeding on Probing for treated implants and implants with no history of peri-implantitis between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* $p<0.05$).

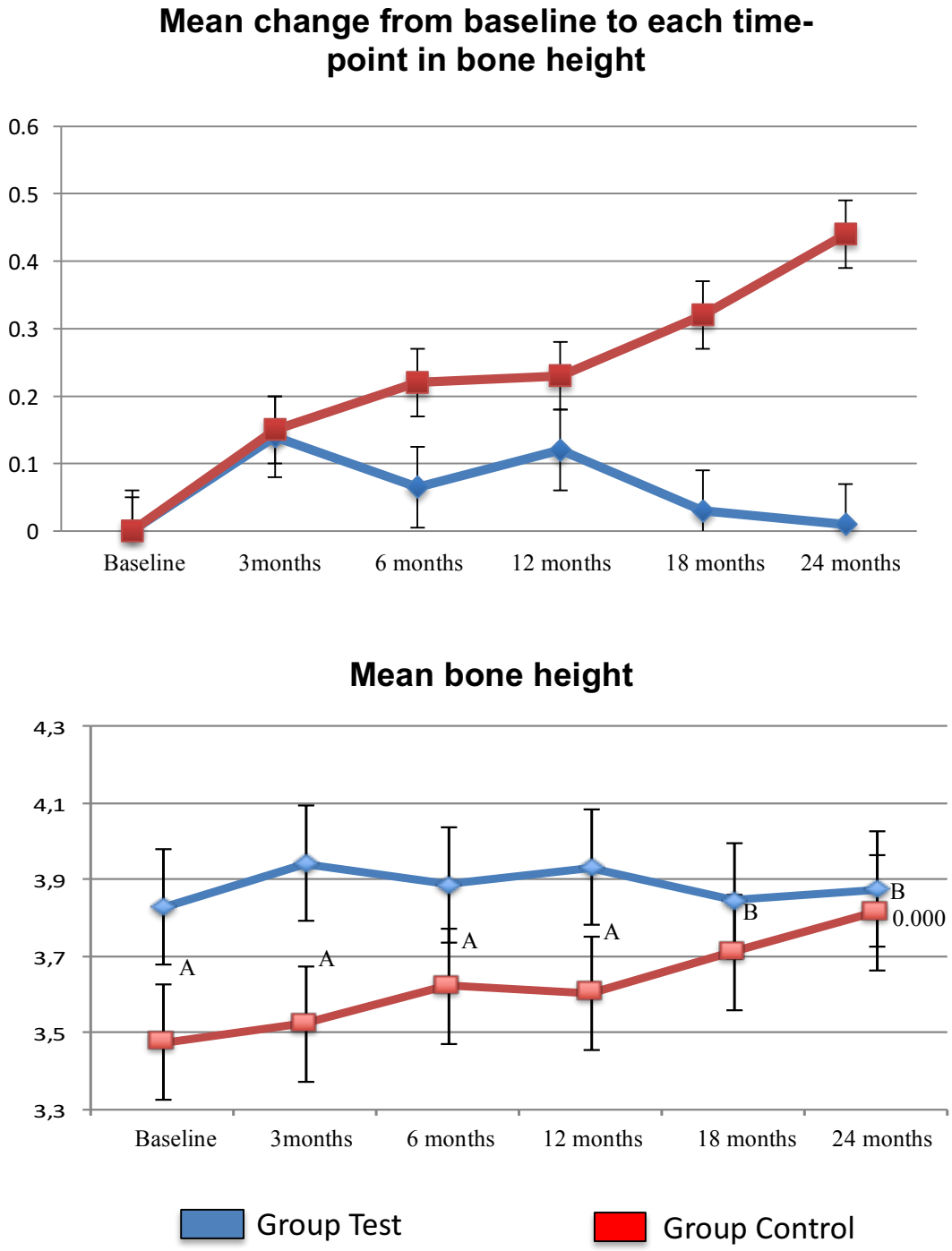


Figure 3. Line chart of the mean Bone Height over the course of the study and mean changes in this parameter from baseline to all follow-up time points. The blue line represents the test group and the red line represents the control group. The significance of differences within each group for mean levels of bone height and the changes between baseline and the other time-points was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center ($p<0.05$).

Table 4. Mean % (± SD) sites gaining or loosing ≥ 2mm of clinical attachment (CA) between baseline and the follow-up appointments.

Variable	Time	Treated implants			Implants with no history of peri-implantitis		
		Test	Control	p-value	Test	Control	p-value
≥ 2mm CA gain	Baseline - 3 months	11.9 ± 18.9	9.9 ± 16.5	0.556	5.9 ± 11.6	2.8 ± 5.8	0.180
	Baseline - 6 months	12.9 ± 17.6	12.3 ± 15.3	0.835	6.9 ± 9.9	3.4 ± 6.9	0.119
	Baseline - 12 months	15.9 ± 18.3	11.4 ± 14.9	0.173	9.0 ± 12.3	3.8 ± 6.0	0.039
	Baseline - 18 months	21.0 ± 24.9	11.0 ± 19.6	**0.025**	9.1 ± 12.5	6.3 ± 10.4	0.337
	Baseline - 24 months	16.7 ± 25.0	8.6 ± 13.1	**0.041**	9.6 ± 13.7	5.3 ± 9.6	0.157
≥ 2mm CA loss	Baseline - 3 months	7.9 ± 12.2	12.3 ± 20.3	0.194	6.6 ± 10.9	6.9 ± 16.8[a]	0.990
	Baseline - 6 months	6.3 ± 9.9	11.9 ± 16.2	**0.038**	7.0 ± 11.2	6.7 ± 11.5 [a]	0.919
	Baseline - 12 months	8.8 ± 14.2	9.0 ± 15.1	0.990	9.5 ± 16.0	11.0 ± 15.2 [b]	0.709
	Baseline - 18 months	9.6 ± 13.8	14.6 ± 20.3	0.150	10.4 ± 16.9	10.1 ± 12.6 [b]	0.573
	Baseline - 24 months	12.0 ± 15.7	18.8 ± 22.1	0.080	10.9 ± 15.9	11.3 ± 12.4 [b]	0.865

The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA, adjusted for baseline mean values and treatment center.

SD: standard deviation; %: percentage.

Table 5. Mean (± SEM) % of sites for treated implants in different Probing Depth (PD) categories over the course of the study.

Variable	Time-point	Groups		p-value
		Test	Control	
PD≥5mm	Baseline	2.92 ± 5.25[a]	3.52 ± 5.47 [a]	0.573
	3 months	2.54 ± 4.73 [a]	2.24 ± 3.23 [a]	0.706
	6 months	1.56 ± 4.04 [a]	2.13 ± 3.10 [b]	0.426
	12 months	1.77 ± 4.41 [a]	1.59 ± 2.78 [b]	0.805
	18 months	0.81 ± 1.66 [b]	1.44 ± 2.64 [b]	0.157
	24 months	1.04 ± 2.40 [b]	1.91 ± 2.67 [b]	0.090
PD≥6mm	Baseline	1.31 ± 4.27 [a]	1.48 ± 2.97	0.815
	3 months	0.94 ± 2.36 [a]	1.11 ± 2.13	0.701
	6 months	0.85 ± 3.53 [a]	0.90 ± 1.78	0.990
	12 months	0.98 ± 3.07 [a]	0.85 ± 1.76	0.795
	18 months	0.23 ± 0.63 [b]	0.80 ± 1.73	**0.034**
	24 months	0.42 ± 1.35 [b]	1.00 ± 1.99	0.090
PD≥7mm	Baseline	0.71 ± 3.63 [a]	0.59 ± 1.55	0.831
	3 months	0.62 ± 2.28 [a]	0.35 ± 1.05	0.431
	6 months	0.40 ± 1.14 [a]	0.46 ± 1.27	0.781
	12 months	0.19 ± 1.04 [b]	0.37 ± 0.10	0.368
	18 months	0.04 ± 0.20 [b]	0.35 ± 0.93	**0.026**
	24 months	0.08 ± 0.40 [b]	0.57 ± 1.67	**0.049**

The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted for baseline mean values and treatment center.

SEM: standard errors of the mean; %: percentage.

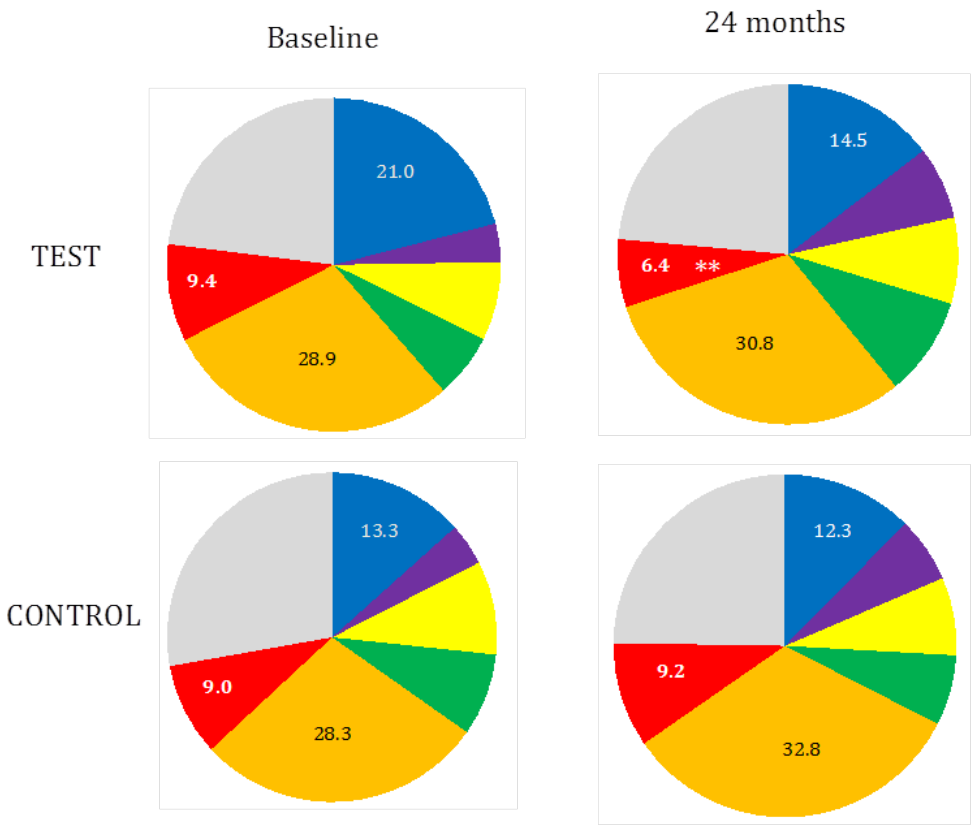


Figure 4. Pie charts of the mean proportions of each microbial complex in the subgingival plaque samples for treated implants. Different colors represent the microbial complexes described by Socransky et al. (1998). The grey color ('Others') represents species that did not fall into any complex, and *Actinomyces spp*. are represented in blue. Significance of differences in mean proportions between baseline and 24 months was sought using Wilcoxon Test (** $p<0.001$) and between groups at each time point using the Mann–Whitney U-test ($p>0.05$).

3.2 Artigo 2

EFFECTS OF A TOOTHPASTE CONTAINING 0.3% TRICLOSAN IN THE PERIODONTAL PARAMETERS OF SUBJECTS WITH HISTORY OF PERI-IMPLANTITIS ENROLLED IN A REGULAR MAINTENANCE PROGRAM: A SECONDARY ANALYSIS OF A 2-YEAR RANDOMIZED CLINICAL TRIAL

Bernal STEWART[1,3], Jamil A. SHIBLI[1], Mauricio ARAUJO[2], Luciene Cristina FIGUEIREDO[1], Fotinos PANAGAKOS[3], Flavia MATARAZO[2], Renata MAIRINK[1], Tatiana ONUMA[1], Marcelo FAVERI[1], Belén RETAMAL-VALDES[1], Magda FERES[1]

[1] Department of Periodontology, Dental Research Division, Guarulhos University, Guarulhos, São Paulo, Brazil

[2] School of Dentistry, Maringa University, Maringa, Paraná, Brazil

[3] Colgate-Palmolive Technology Center, Piscataway, New Jersey, USA

Address for correspondence and reprints *(e-mail can be published)*

Bernal Stewart

909 River Road

Piscatway, New Jersey 08873

Phone: +1-732-878-7597

E-mail: bernal_stewart@colpal.com

ABSTRACT

Aim: To evaluate the clinical effects of a toothpaste containing 0.3% triclosan on the periodontal parameters of subjects that have been treated for peri-implantitis and were enrolled in a regular maintenance program. **Methods**: Subjects presenting at least one implant with peri-implantitis and received surgical anti-infective therapy were selected. Sixty days post-surgery (baseline), subjects were randomized into two groups: (i) toothpaste containing 0.3% triclosan+2.0% Gantrez copolymer+1450 ppm fluoride (test) or (ii) toothpaste containing 1450 ppm fluoride (control), and were instructed to brush with the assigned toothpaste twice/day for 2 years. They received clinical monitoring at baseline, 3, 6, 12, 18 and 24 months, and professional maintenance every 3 months. **Results:** Eighty-eight subjects with natural teeth were enrolled in the study (Test, n= 39; Control, n=49). The test group showed a greater reduction in the percentage of sites exhibiting bleeding on probing (primary outcome) and lower levels of plaque in comparison with the control group after 24 months of brushing with the assigned toothpastes ($p<0.05$). The mean percentage of sites with probing depth ≥ 5mm was reduced over the course of the study only in the test group ($p<0.05$). **Conclusion**: The data of the present study showed that a toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining a healthier periodontal environment around natural teeth of subjects that have been treated for peri-implantitis and were enrolled in a regular maintenance program for 2 years.

Key-words: Periodontal disease; Periodontitis; Toothpaste; Triclosan.

Introduction

The success of periodontal and peri-implant treatments depends on a well-controlled maintenance phase (Axelsson & Lindhe 1981, Drisko 2001, Loesche et al. 2005) that should include anti-infective procedures with the ability to sustain low levels of periodontal/peri-implant pathogens and to maintain the colonization of host-compatible bacterial species (Teles et al. 2006). Although strict professional plaque control performed during and after periodontal treatment improves treatment outcomes (Feres et al. 2009), many patients are not able to effectively remove this biofilm over time (Cumming & Loe 1973, Tonetti et al. 2015). Therefore, a few antimicrobial agents have been used as adjuncts to mechanical oral hygiene procedures in order to improve oral biofilm accumulation in subjects under periodontal/peri-implant maintenance (Yates et al. 1993, Rosling et al. 1997, Ramberg et al. 2009, Costa et al. 2013, Triratana et al. 2015).

To enhance the effect of daily mechanical tooth cleaning, antimicrobial agents such as triclosan, fluoride, cetylpyridinium chloride, clorhexidine, essential oils and herbal extract (i.e. aloe vera and propolis) have been incorporated into dentifrices and mouthrinse preparations (Jenkins et al. 1993, Yates et al. 1993, Kjaerheim et al. 1996, Botushanov et al. 2001, Archila et al. 2005, Muller et al. 2006, Mateu et al. 2008, Ramberg et al. 2009, Boneta et al. 2010, de Andrade Meyer et al. 2010, Mankodi et al. 2011, Pradeep et al. 2012, Costa et al. 2013, Riley & Lamont 2013, Kang et al. 2015, Triratana et al. 2015). Among these, triclosan has shown to be one of the most effective compounds due to its good antimicrobial activity (Fine et al. 1998, Xu et al. 2005, Haraszthy et al. 2010). A comprehensive review summarizing several clinical studies of at least 6 months of duration showed that a dentifrice containing 0.3% triclosan was more effective than regular toothpastes in reducing supragingival plaque, calculus, gingivitis and caries (Volpe et al. 1996). In addition, a recent Cochrane systematic review (Riley & Lamont 2013) showed moderate evidence for the effect of toothpastes containing triclosan on the reduction of dental biofilm and gingival inflammation when compared to toothpastes without triclosan.

Despite the good scientific evidence supporting the benefits of triclosan-containing dentifrices in controlling biofilm formation and maintaining gingival health, only one study to date has evaluated the effects of these toothpastes during a regular professional maintenance program, in smokers (Kerdvongbundit et al. 2003).

Therefore, the aim of this study was to evaluate the clinical effects of a toothpaste containing 0.3% triclosan on the periodontal parameters of a population comprising of mainly non-smokers subjects that have been treated for peri-implantitis and were enrolled in a regular maintenance program.

Material and Methods

The Material and Methods were presented in details in the preceding study (Stewart et al. 2017). The main aspects of the study design are summarized below.

Power calculation and primary outcome variable

This study presents the data for natural teeth of a Randomized Clinical Trial (RCT) (Stewart et al. 2017), designed and powered to compare the clinical effects of a toothpaste containing 0.3% triclosan in implants that have been treated for peri-implantitis and enrolled in a regular maintenance program. Therefore, a post hoc analysis was conducted to determine the actual power of the secondary analysis presented in this manuscript. Considering a difference of 11 percentage points between the two groups for the mean changes from Baseline to 24 months in the mean percentage of sites with Bleeding on Probing (BOP) (primary outcome variable) (Control group 1.4%, Test group 12.4%), a standard deviation of 12.9%, a sample size of 88 subjects (39 and 49 subjects in Test and Control groups, respectively) and an α of 0.05, the power of the present analysis was 95%.

Subject population and inclusion/exclusion criteria

Study participants were selected from the population referred to the Center for Clinical Trials of Guarulhos University (Guarulhos, SP, Brazil) and the Diagnostic Clinic of State University of Maringa (Maringa, PR, Brazil). Subjects that met the study inclusion and exclusion criteria were invited to participate into the study. Detailed medical, periodontal and dental/implant histories were obtained. All eligible subjects were informed of the nature, potential risks and benefits of their participation in the study and signed a Term of Informed Consent. The Clinical Research Ethics Committee of Guarulhos University and State University of Maringa approved the study protocol (CAAE – 0007.0.132.000-10 and 205/2010 - 049/2013, respectively).

The inclusion criteria were as follows: males and females aged 18 to 70 years-old, in general good health, with a minimum of 1 dental implant in function for at least one year with untreated peri-implantitis defined as: probing depth (PD) ≥ 5 mm, BOP or suppuration, radiographic bone loss involving 3 mm from the upper border of the intrabony portion of the implant. The exclusion criteria were as follows: untreated periodontitis (defined as ≥ 6 sites with PD ≥ 5 mm) or individuals that received periodontal treatment within three months prior to entering the study, inability to perform proper supragingival plaque control (e.g. due to improper prosthesis design or lack of skills), diabetes, pregnancy, nursing, history of allergies to triclosan, fluoride or any other ingredient of oral care products, alcohol or drug abuse, any systemic diseases that could affect post-operative healing or that required antibiotic premedication for routine dental therapy, long-term use of mouthrinses, anti-inflammatory medications or any other drug that could interfere with the study outcomes within three months prior to entering the study, antibiotics use within six months prior to entering the study and participation in any other clinical study within three months prior to entering the study.

Experimental design and treatment protocol

This Phase III, randomized, parallel, double blinded, two-center clinical study was designed in two phases, a surgical and a maintenance phase. Before the study started, the two coordinators (M.Fe. and M.A.) used a computer program (www.sealedenvelope.com) to randomly allocate subjects (1:1 allocation ratio in blocks of four) into two groups of subjects that would brush twice a day with a toothpaste containing (i) 0.3% triclosan, 2.0% Gantrez copolymer + 1450 ppm fluoride (Test Group) or (ii) 1450 ppm fluoride (Control Group).

At the beginning of the study, all subjects received oral hygiene instructions, full-mouth supragingival plaque removal and prophylaxis. Subgingival scaling was administered to sites exhibiting a PD ≥ 4 mm. Partial and total fixed suprastructures on implants were removed before treatment. They also received oral health instructions (OHI) and were given: a soft bristle adult toothbrush, dental floss, and interdental toothbrushes, according to their individual needs. Subsequently, the implants with peri-implantitis received anti-infectious treatment (treated implants) by means of open-flap mechanical anti-infective debridement and bicarbonate jet (Jet

Sonic System), as described in Stewart et al (2017). Analgesics were prescribed to all subjects and they were instructed to rinse with a chlorexidine mouthwash for 7 days.

Subjects returned to the clinic 60 days after the surgeries for clinical and microbiological monitoring (baseline) and to receive the toothpaste according to their experimental treatment group (Test or Control). They received a regular adult soft bristles toothbrush (Colgate Palmolive, Brazil) as well as dental floss (Colgate Palmolive, Brazil) and interdental toothbrushes (Colgate Palmolive, Brazil), according to their individual needs. They were instructed to brush their teeth for one minute twice a day (morning and evening) using only the toothbrush and toothpaste provided. All subjects returned for the maintenance visits every 3 months and received OHI, supragingival and subgingival biofilm removal and a prophylaxis. The used products (brushes and toothpastes) were replaced at all maintenance visits.

Colgate Palmolive (São Paulo, Brazil) prepared the Test and Control toothpastes and placed them in opaque identical tubes labeled-coded for each group (F or P, respectively). At each site, the study coordinators (M.Fe. and M.A.) received the toothpastes/toothbrushes and placed them in indistinguishable plastic bags numbered from 1 to 53 according to the randomization list, which was also labeled-coded (F or P). This process was done to ensure allocation concealment. All study personnel were blinded as to products allocation. Code breaking was done after data analysis.

Clinical monitoring

Three calibrated examiners (Stewart et al. 2017), two from Guarulhos University (T.O and R.M.) and one from the State University of Maringa (F.M.) performed all clinical examinations. The following parameters were recorded at 6 sites per tooth/implants excluding third molars, using a North Carolina periodontal probe (Hu-Friedy, Chicago, IL, USA): Plaque Index (PI) (Turesky et al. 1970 , Quigley & Hein 1962) (The plaque was disclosed using a disclosing solution and recorded as follows: score 0 = absence of plaque; score 1 = separate flecks of plaque on the cervical margin; score 2 = a thin, continuous band of plaque [up to 1mm] at the cervical margin of the tooth; score 3 = a band of plaque wider than 1mm, but covering less than 1/3 of the tooth crown; score 4 = plaque covering at least 1/3, but less than 2/3 of the crown of the tooth; score 5 = plaque covering 2/3-crown or more

of the crown of the tooth), Gingival Index (GI) (Loe & Silness 1963), presence or absence of BOP and suppuration, PD (mm) and relative clinical attachment level (CAL) (distance in mm from the cement-enamel junction/implant shoulder to the most apical portion of the sulcus or periodontal/peri-implantar pocket). The clinical monitoring was performed at baseline, 3, 6, 12, 18 and 24 months.

Monitoring of compliance and adverse events

At each maintenance visit the subjects were asked to return the used toothbrushes and the toothpaste tubes in order to monitoring compliance. The tubes were checked for remaining paste and the condition of the toothbrushes were also evaluated. The examiners asked the subjects if they had experienced any undesirable effect that could be associated with the use of the toothpastes. If any adverse events were observed, the subject should be instructed to discontinue the toothpaste and withdrawn from the study.

Statistical analysis

The significance of differences between the two groups at baseline for mean number (and percentage) of subjects presenting different numbers of sites with PD and CAL ≥5mm at pre-baseline and baseline time-points was sought by Chi-square, and for mean number of sites with PD and CAL ≥ 5 mm at each time point was sought using Student T-test.

The significance of differences within each group over time was assessed by repeated measures ANOVA and Tukey's multiple comparison tests. The significance of differences between the two treatment groups from baseline to the other time points was sought using ANCOVA adjusted for baseline values and study center. The data were evaluated using intention-to-treat analysis with last observation carried forward. The level of significance was set at 5%.

The effect sizes (ES) between groups (Cohen 1988) were calculated using "reduction from baseline to 24 months in the percentage of sites exhibiting BOP" and the following categories: (i) small ES: 0.20 (0-0.39), (ii) moderate ES: 0.50 (0.40-0.79) and (iii) large ES: ≥0.80. Subsequently, the 0.2 and 0.5 Minimal Important Differences (MID) were also calculated based on the pooled standard deviation of the

groups. Finally, using the distribution-based method, the clinical relevance was scored as not clinically relevant, potentially clinically relevant or clinically relevant, based on the relationship among the mean difference of the variable, MIDs and ES (Armijo-Olivo et al. 2011).

Results

Subject retention, adverse effects and compliance

The study was conducted between June 2010 and December 2014. Figure 1 presents the flow diagram of the study design. Two thousand five hundred subjects were assessed for eligibility and 109 entered the study at the Pre-baseline phase and received surgeries (Test Group, n=53 subjects; Control Group, n=56 subjects). Sixty days after surgeries, 102 subjects entered the Experimental Phase and 88 subjects presenting natural teeth were included in the present analysis (Test Group, n=39; Control group, n=49). From these, three subjects and two subjects were lost because did not return to one of the follow-up visits. Thirty-six and 47 subjects presenting in the Test and Control groups, respectively, completed the study up to 24 months. No adverse events were reported and lack of compliance was not detected. All subjects returned the used and unused study products at the maintenance visits.

Clinical findings

No statistically significant differences were observed for clinical parameters and demographic characteristics of the population studied at baseline (Stewart et al. 2017). Table 1 presents the distribution of the population studied according to the mean number of deep sites at the pre-baseline and baseline phases. 59% and 45% of the subjects in the Test and Control groups, respectively, had at least one site with PD≥5mm before the study started. The population studied had an average of ~13 sites with CAL ≥5mm before the beginning of the study.

Figures 2a and 2b present the comparison between the two groups for the changes occurring in BOP, PI, GI, PD and CAL, between baseline and each follow-up time point, and Table 2 shows the mean values of these clinical parameters at all time points. The mean percentage of sites showing gingival inflammation was

significantly decreased in both groups over the course of the study, while the percentage of sites with BOP was statistically significantly reduced only in the test group (Table 2). In addition, the reduction in the percentage of sites with BOP between baseline and 12, 18 and 24 months (primary outcome variable) was significantly greater in the Test than in the Control group, as well as the reduction in PI between baseline and 6, 12, 18 and 24 months (Figure 2a). The changes occurring in GI, PD and CAL were not statistically significant over the course of the study within each group, or between groups at each post-baseline time point (Figures 2a and 2b).

Only the test group exhibited a statistically significant reduction in the mean number of sites with PD ≥ 5mm over the course of the study ($p<0.05$). There were no statistically significant reductions in the mean number of sites with PD ≥ 6mm and PD ≥ 7mm in the two groups from baseline to 24 months (Table 4).

Table 3 presents an analysis of clinical relevance using the variable “mean reduction in the percentage of sites with BOP from baseline to 24 months” (Armijo-Olivo et al., 2011) and distribution-based methods. The results indicated that the difference observed between Test and Control group for this parameter (Figure 2a) was clinically relevant.

DISCUSSION

The data of the present study showed that a toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining a healthier periodontal environment around natural teeth of subjects presenting at least one implant that had been treated for peri-implantitis, and who were enrolled in a regular professional periodontal/peri-implant maintenance program. Subjects that brushed with the triclosan toothpaste showed a greater reduction in the percentage of sites with BOP between baseline and 24 months than those brushing with a regular toothpaste (primary outcome variable) ($p<0.05$). These results have shown to be clinically relevant (Table 4). In addition, the reduction in PI and in the percentage of sites with PD≥5 mm was more efficiently reduced in the triclosan group over the course of the study.

Although we cannot assure that all subjects included in this study had a history of periodontitis, the elevated mean number of sites with CA loss at baseline (Table 1) suggests that many subjects might have had previous periodontal treatment. In addition, all subjects included in the present study had a history of peri-implantitis. A few previous studies with follow-up periods of 1 year or more have evaluated the effects of triclosan toothpastes in subjects with history of periodontitis (Rosling et al. 1997, Ellwood et al. 1998, Cullinan et al. 2003, Kerdvongbundit & Wikesjö et al. 2003) and the overall data of these studies suggested a clinical beneficial effect of the triclosan toothpastes in reducing CA loss and BOP when compared with regular fluoride toothpastes. However, none of these studies included a regular periodontal maintenance program with supra and subgingival professional interventions at regular intervals. Rosling et al. (1997) followed a population with adult patients with history of periodontitis for a period of 3 years. Subjects brushed with a toothpaste containing or not containing triclosan and received periodontal maintenance that included only OHI. The authors observed that the dentifrice containing triclosan was more effective than the regular dentifrice in preventing further bone loss and in reducing PD, over a period of 3 years. As oppose to the protocol used by Rosling et al. (1997) that did not include any professional intervention during the maintenance phase, subjects in the present study received meticulous supragingival and subgingival biofilm removal every 3 months. Thus, the benefits of triclosan in the present study were beyond those obtained with a meticulous professional maintenance program.

In agreement with our data, three previous systematic reviews including studies with at least 6 months of follow-up that evaluated adults that brushed with toothpastes containing triclosan have confirmed a statistically significant benefit of the triclosan toothpaste in plaque and gingivitis when compared with standard fluoride toothpastes (Davies et al. 2004, Hioe & van der Weijden 2005, Gunsolley 2010). In addition, a recent systematic review of "The Cochrane Collaboration" (Riley & Lamont 2013) evaluated the weight of evidence for the long-term benefits of triclosan-containing toothpastes on caries, gingivitis and dental biofilm control. The authors showed moderate evidence of greater benefits for these dentifrices on dental biofilm reduction and gingival inflammation when compared with the effects of fluoride-containing toothpastes, without triclosan.

The beneficial effects of triclosan on supragingival parameters such as on plaque accumulation described in the above-mentioned reviews and in the present study might be explained by the triclosan's well known antimicrobial properties (Fine et al. 1998, Xu et al. 2005, Haraszthy et al. 2010). Indeed, subjects in the triclosan group showed statistically significant reductions in PI over the course of the study and lower plaque accumulation when compared to the control group at 6, 12, 18 and 24 months. Triclosan is a nonionic bisphenolic molecule with a broad spectrum antibacterial activity (Davies 2008, Sanz et al. 2013). In conventional toothpastes formulation triclosan stays in the mouth for a few hours. However, manufacturers have adopted different approaches, such as the addition of a copolymer, to increase its uptake and retention to oral surfaces (Davies 2008), as the formulation used in this study that combined 0.3% triclosan and 2.0% Gantrez copolymer.

The benefits of triclosan on subgingival parameters, such as in BOP and in the percentage of residual sites are more intriguing and might be associated with indirect effects obtained from supragingival plaque control and anti-inflammatory properties (Gaffar et al. 1995, Modeer et al. 1996, Panagakos et al. 2005). The control of supragingival plaque and the reduction of inflammation reduce availability of nutrients for bacterial growth, leading to a more beneficial subgingival microbial profile, and consequently, to a greater stability in clinical periodontal parameters (Socransky & Haffajee 2002, Feres et al. 2009). Indeed, the implants treated for peri-implantitis from the test group in the present study showed lower levels of red complex pathogens in comparison with those from the control group at 24 months (Stewart et al. 2017). Another important effect of the triclosan in this study was the significant reduction in the mean percentage of sites with PD≥5 mm over the course of the study. This effect provides periodontal stability and help to reduce the risk for development of peri-implantiits (Renvert & Quirynen 2015), a desirable effect, especially in this population that had been treated for peri-implantitis.

The main strengths of this study were to assess the effects of triclosan in a very well maintained population following a meticulous professional periodontal/peri-implant maintenance program, and the follow-up period of 2 years. Moreover, to our knowledge this is one of the few studies to present an analysis of clinical relevance for the primary outcome. One limitation of this study was to not have included a microbiological analysis of the supragingival and/or subgingival plaque, which would

have allowed a deeper evaluation of the effects of triclosan in the microbial profile and could help to support the clinical differences observed between the two treatment groups.

In conclusion, the data of the present study showed that a toothpaste containing 0.3% triclosan was more effective than a regular fluoride toothpaste in maintaining a healthier periodontal environment around natural teeth of subjects that have been treated for peri-implantitis and who were enrolled in a regular maintenance program for 2 years.

Acknowledgments

This study was supported by Colgate-Palmolive, Technology Center, (Piscataway, New Jersey, USA) and Latin America Oral Health Association (LAOHA).

REFERENCES

Archila, L., He, T., Winston, J. L., Biesbrock, A. R., McClanahan, S. F. & Bartizek, R. D. (2005) Antigingivitis efficacy of a stabilized stannous fluoride/sodium hexametaphosphate dentifrice in subjects previously nonresponsive to a triclosan/copolymer dentifrice. *Compendium of continuing education in dentistry* **26,** 12-18.

Armijo-Olivo, S., Warren, S., Fuentes, J. & Magee, D. J. (2011) Clinical relevance vs. statistical significance: Using neck outcomes in patients with temporomandibular disorders as an example. *Manual Therapy* **16,** 563-572.

Axelsson, P. & Lindhe, J. (1981) Effect of controlled oral hygiene procedures on caries and periodontal disease in adults. Results after 6 years. *Journal of Clinical Periodontology* **8,** 239-248.

Boneta, A. E., Aguilar, M. M., Romeu, F. L., Stewart, B., DeVizio, W. & Proskin, H. M. (2010) Comparative investigation of the efficacy of triclosan/copolymer/sodium fluoride and stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrices for the control of established supragingival plaque and gingivitis in a six-month clinical study. *The Journal of Clinical Dentistry* **21,** 117-123.

Botushanov, P. I., Grigorov, G. I. & Aleksandrov, G. A. (2001) A clinical study of a silicate toothpaste with extract from propolis. *Folia Medica (Plovdiv)* **43,** 28-30.

Cohen, J. (1988) The concepts of power analysis. In: *Statistical power analysis for the behavioral sciences*, (ed.) C. J, pp. 1-17. Hillsdale, New Jersey: Academic Press, Inc.

Costa, X., Laguna, E., Herrera, D., Serrano, J., Alonso, B. & Sanz, M. (2013) Efficacy of a new mouth rinse formulation based on 0.07% cetylpyridinium chloride in the control of plaque and gingivitis: a 6-month randomized clinical trial. *Journal of Clinical Periodontology* **40,** 1007-1015.

Cullinan, M.P., Westerman, B., Hamlet, S.M., Palmer, J.E., Faddy, M.J. & Seymour, G.J. (2003) The effect of a triclosan-containing dentifrice on the progression of periodontal disease in an adult population. *Journal of Clinical Periodontology* **30**; 414–419.

Cumming, B. R. & Loe, H. (1973) Consistency of plaque distribution in individuals without special home care instruction. *Journal of Periodontal Research* **8,** 94-100.

Davies, R. M. (2008) Toothpaste in the control of plaque/gingivitis and periodontitis. *Periodontology 2000* **48**, 23-30.

Davies, R. M., Ellwood, R. P. & Davies, G. M. (2004) The effectiveness of a toothpaste containing triclosan and polyvinyl-methyl ether maleic acid copolymer in improving plaque control and gingival health: a systematic review. Journal of Clinical Periodontology **31**, 1029-1033.

de Andrade Meyer, A. C., de Mello Tera, T., da Rocha, J. C. & Jardini, M. A. (2010) Clinical and microbiological evaluation of the use of toothpaste containing 1% chlorhexidine and the influence of motivation on oral hygiene in patients with motor deficiency. *Special Care in Dentistry* **30,** 140-145.

Drisko, C. H. (2001) Nonsurgical periodontal therapy. *Periodontology 2000* **25,** 77-88.

Ellwood, R.P., Worthington, H.V., Blinkhorn, A.S., Volpe, A.R. & Davies, R.M. (1998) Effect of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents. *Journal of Clinical Periodontology* **25(5)**:363-7.

Feres, M., Gursky, L. C., Faveri, M., Tsuzuki, C. O. & Figueiredo, L. C. (2009) Clinical and microbiological benefits of strict supragingival plaque control as part of the active phase of periodontal therapy. *Journal of Clinical Periodontology* **36,** 857-867.

Fine, D. H., Furgang, D., Bonta, Y., DeVizio, W., Volpe, A. R., Reynolds, H., Zambon, J. J. & Dunford, R. G. (1998) Efficacy of a triclosan/NaF dentifrice in the control of plaque and gingivitis and concurrent oral microflora monitoring. *American Journal of Dentistry* **11,** 259-270.

Gaffar, A., Scherl, D., Afflitto, J. & Coleman, E. J. (1995) The effect of triclosan on mediators of gingival inflammation. *Journal of Clinical Periodontology* **22**, 480-484.

Gunsolley, J. C. (2010) Clinical efficacy of antimicrobial mouthrinses. *Journal of Dentistry* **38 Suppl 1**, S6-10.

Haraszthy, V. I., Zambon, J. J. & Sreenivasan, P. K. (2010) Evaluation of the antimicrobial activity of dentifrices on human oral bacteria. *The Journal of Clinical Dentistry* **21,** 96-100.

Hioe, K. P. & van der Weijden, G. A. (2005) The effectiveness of self-performed mechanical plaque control with triclosan containing dentifrices. *International Journal of Dental Hygiene* **3**, 192-204.

Jenkins, S., Addy, M. & Newcombe, R. (1993) The effects of a chlorhexidine toothpaste on the development of plaque, gingivitis and tooth staining. *Journal of Clinical Periodontology* **20,** 59-62.

Kang, J. H., Jang, Y. J., Kim, D. J. & Park, J. W. (2015) Antimicrobial effectiveness of cetylpyridinium chloride and zinc chloride-containing mouthrinses on bacteria of halitosis and peri-implant disease. *The International Journal of Oral & Maxillofacial Implants* **30,** 1341-1347.

Kerdvongbundit, V. & Wikesjö, U.M. (2003) Effect of triclosan on healing following non-surgical periodontal therapy in smokers. *Journal of Clinical Periodontology* **30**(**12**):1024-1030.

Kjaerheim, V., Skaare, A., Barkvoll, P. & Rolla, G. (1996) Antiplaque, antibacterial, and anti-inflammatory properties of triclosan mouthrinses in combination with zinc citrate or polyvinylmethylether maleic acid (PVM-MA) copolymer. *European Journal of Oral Sciences* **104,** 529-534.

Loe, H. & Silness, J. (1963) Periodontal Disease in Pregnancy. I. Prevalence and Severity. *Acta Odontologica Scandinavica* **21,** 533-551.

Loesche, W. J., Giordano, J. R., Soehren, S. & Kaciroti, N. (2005) The nonsurgical treatment of patients with periodontal disease: results after 6.4 years. *General Dentistry* **53,** 298-306; quiz 307.

Mankodi, S., Chaknis, P., Panagakos, F. S., DeVizio, W. & Proskin, H. M. (2011) Comparative investigation of a dentifrice containing triclosan/copolymer/sodium fluoride and specially-designed silica and a dentifrice containing 0.243% sodium fluoride in a silica base for the control of established supra-gingival plaque and gingivitis: a 6-month clinical study. *American Journal of Dentistry* **24 Spec No A,** 21A-27A.

Mateu, F. A., Boneta, A. E., DeVizio, W., Stewart, B. & Proskin, H. M. (2008) A clinical investigation of the efficacy of two dentifrices for controlling established supragingival plaque and gingivitis. *The Journal of Clinical Dentistry* **19,** 85-94.

Modeer, T., Bengtsson, A. & Rolla, G. (1996) Triclosan reduces prostaglandin biosynthesis in human gingival fibroblasts challenged with interleukin-1 in vitro. *Journal of Clinical Periodontology* **23**, 927-933.Moran, J., Addy, M. & Newcombe, R. (1991) Comparison of an herbal toothpaste with a fluoride toothpaste on plaque and gingivitis. *Clinical preventive dentistry* **13,** 12-15.

Muller, H. P., Barrieshi-Nusair, K. M., Kononen, E. & Yang, M. (2006) Effect of triclosan/copolymer-containing toothpaste on the association between plaque and gingival bleeding: a randomized controlled clinical trial. *Journal of Clinical Periodontology* **33,** 811-818.

Panagakos, F. S., Volpe, A. R., Petrone, M. E., DeVizio, W., Davies, R. M. & Proskin, H. M. (2005) Advanced oral antibacterial/anti-inflammatory technology: A comprehensive review of the clinical benefits of a triclosan/copolymer/fluoride dentifrice. *The Journal of Clinical Dentistry* **16 Suppl**, S1-19.

Pradeep, A. R., Agarwal, E. & Naik, S. B. (2012) Clinical and microbiologic effects of commercially available dentifrice containing aloe vera: a randomized controlled clinical trial. *Journal of Periodontology* **83,** 797-804.

Quigley, G. A. & Hein, J. W. (1962) Comparative cleansing efficiency of manual and power brushing. *Journal of American Dental Association* **65**, 26–29.

Ramberg, P., Lindhe, J., Botticelli, D. & Botticelli, A. (2009) The effect of a triclosan dentifrice on mucositis in subjects with dental implants: a six-month clinical study. *The Journal of Clinical Dentistry* **20,** 103-107.

Renvert, S. & Quirynen, M. (2015) Risk indicators for peri-implantitis. A narrative review. *Clinical Oral Implant Research* **26** Suppl 11, 15-44.

Riley, P. & Lamont, T. (2013) Triclosan/copolymer containing toothpastes for oral health. *The Cochrane database of systematic reviews***,** CD010514. doi:10.1002/14651858.CD010514.pub2.

Rosling, B., Wannfors, B., Volpe, A.R., Furuichi, Y., Ramberg, P. & Lindhe, J. (1997) The use of a triclosan/copolymer dentifrice may retard the progression of periodontitis. *Journal of Clinical Periodontology* **24(12)**:873-880.

Sanz, M., Serrano, J., Iniesta, M., Santa Cruz, I. & Herrera, D. (2013) Antiplaque and antigingivitis toothpastes. *Monographs in Oral Science* **23**, 27-44.

Socransky, S.S. & Haffajee, A.D. (2002) Dental biofilms: difficult therapeutic targets. *Periodontology 2000* **28**:12-55.

Stewart, B., Araujo, M., Figueiredo, L., Panagakos, F., Matarazo, F., Shibli, J., Mairink, R., Onuma, T., Faveri, M., Retamal-Valdes, B., Feres, M. (2017) Effects of a toothpaste containing 0.3% triclosan in the periodontal parameters of subjects with history of peri-implantitis enrolled in a regular maintenance program: a secondary analysis of a 2-year randomized clinical trial. “In preparation”.

Teles, R. P., Haffajee, A. D. & Socransky, S. S. (2006) Microbiological goals of periodontal therapy. *Periodontology 2000* **42,** 180-218.

Tonetti, M. S., Eickholz, P., Loos, B. G., Papapanou, P., van der Velden, U., Armitage, G., Bouchard, P., Deinzer, R., Dietrich, T., Hughes, F., Kocher, T., Lang, N. P., Lopez, R., Needleman, I., Newton, T., Nibali, L., Pretzl, B., Ramseier, C., Sanz-Sanchez, I., Schlagenhauf, U. & Suvan, J. E. (2015) Principles in prevention of periodontal diseases: Consensus report of group 1 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. *Journal of Clinical Periodontology* **42 Suppl 16,** S5-11.

Triratana, T., Kraivaphan, P., Amornchat, C., Mateo, L. R., Morrison, B. M., Jr., Dibart, S. & Zhang, Y. P. (2015) Comparing three toothpastes in controlling plaque and gingivitis: A 6-month clinical study. *American Journal of Dentistry* **28,** 68-74.

Turesky, S., Gilmore, N. D. & Glickman, I. (1970) Reduced plaque formation by the chloromethyl analogue of victamine C. *Journal of Periodontology* **41,** 41-43.

Volpe, A. R., Petrone, M. E., De Vizio, W., Davies, R. M. & Proskin, H. M. (1996) A review of plaque, gingivitis, calculus and caries clinical efficacy studies with a fluoride dentifrice containing triclosan and PVM/MA copolymer. *The Journal of Clinical Dentistry* **7 Suppl,** S1-S14.

Xu, T., Deshmukh, M., Barnes, V. M., Trivedi, H. M., Du-Thumm, L., Richter, R. & Cummins, D. (2005) Analysis of the antibacterial activity and plaque control benefit of colgate total dentifrice via clinical evaluation and real-time polymerase chain reaction. *The Journal of Clinical Dentistry* **16,** 117-122.

Yates, R., Jenkins, S., Newcombe, R., Wade, W., Moran, J. & Addy, M. (1993) A 6-month home usage trial of a 1% chlorhexidine toothpaste (1). Effects on plaque, gingivitis, calculus and toothstaining. *Journal of Clinical Periodontology* **20,** 130-138.

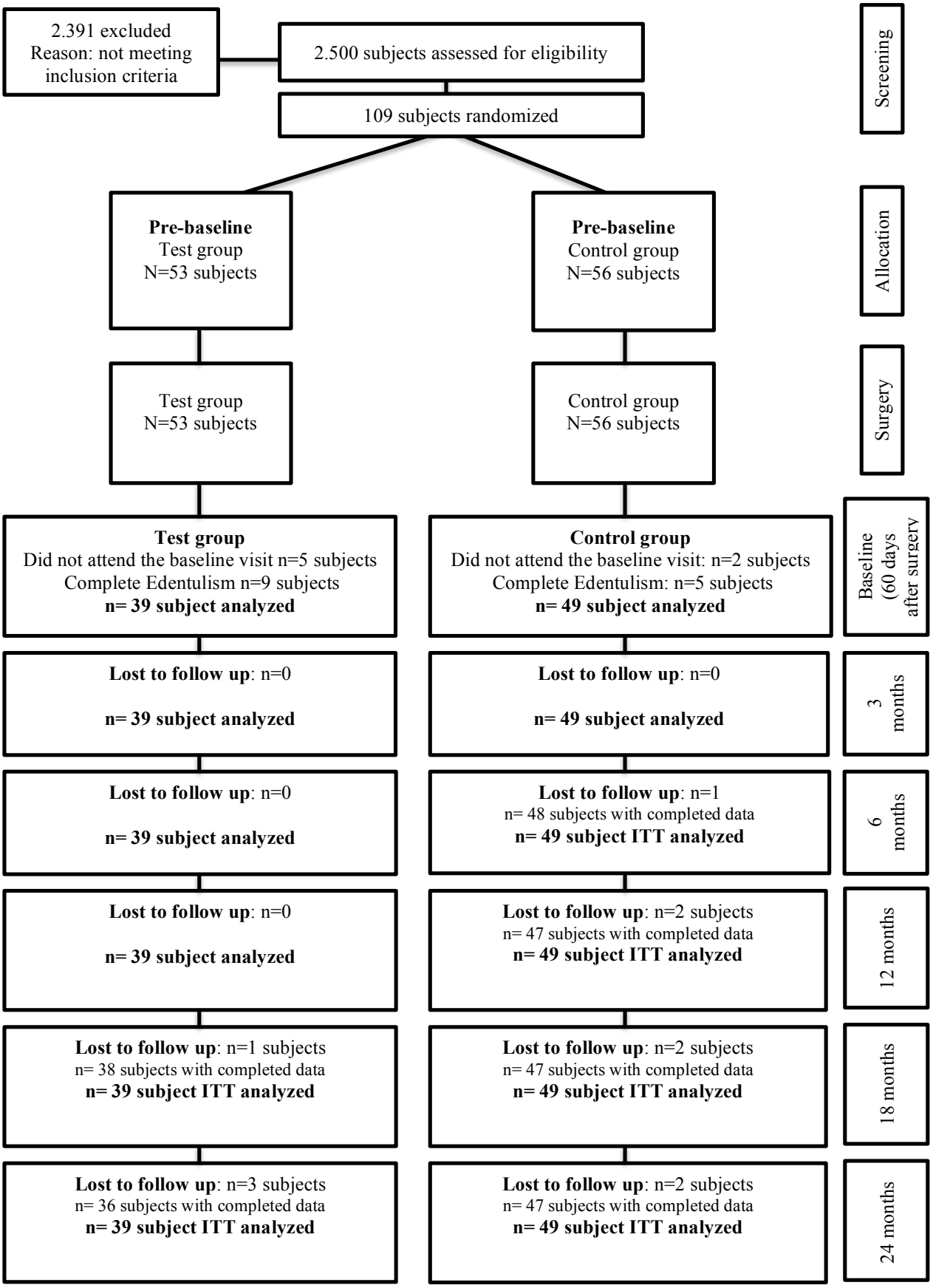


Figure 1. Study Flow Chart

Table 1. Mean (± SD) number (and percentage) of subjects presenting different numbers of sites with probing depth (PD) and clinical attachment level (CAL) ≥5mm at pre-baseline and baseline time-points, and mean number (± SD) of sites with PD and CAL ≥ 5 mm at each time point.

Time-point	Parameter		Groups		p-value
			Test (n=39)	Control (n=49)	
PRE-BASELINE	Number of sites PD≥5mm	≥ 1	23 (59%)	22 (45%)	
		≥ 2	15 (38%)	19 (39%)	
		≥ 3	8 (21%)	17 (35%)	#p=0.326
		≥ 4	8 (21%)	13 (26%)	
		mean	1.54 ± 1.85	3.16 ± 5.87	&p>0.05
	Number of sites CAL≥5mm	≥ 1	35 (90%)	42 (86%)	
		≥ 2	32 (82%)	38 (77%)	
		≥ 3	29 (59%)	37 (75%)	#p=0.999
		≥ 4	29 (59%)	35 (71%)	
		mean	13.85 ± 17.09	13.16 ±14.92	&p>0.05
BASELINE	Number of sites PD≥5mm	≥ 1	15 (38%)	16 (33%)	
		≥ 2	10 (26%)	11 (22%)	
		≥ 3	9 (23%)	8 (16%)	#p=0.928
		≥ 4	7 (18%)	5 (10%)	
		mean	1.31 ± 2.15	1.50 ± 4.76	&p>0.05
	Number of sites CAL≥5mm	≥ 1	32 (82%)	42 (86%)	
		≥ 2	29 (59%)	36 (73%)	
		≥ 3	27 (69%)	31 (63%)	#p=996
		≥ 4	26 (67%)	31 (63%)	
		mean	12.31 ± 15.21	12.33 ±16.87	&p>0.05

The significance of differences between groups for number (and percentage) of subjects presenting different numbers of sites with probing depth (PD) and clinical attachment level (CAL) was sought by Chi-square (# = $p<0.05$) and mean number of sites with PD and CAL ≥ 5 mm at each time point by using Student T-test T-Test (& = $p>0.05$).

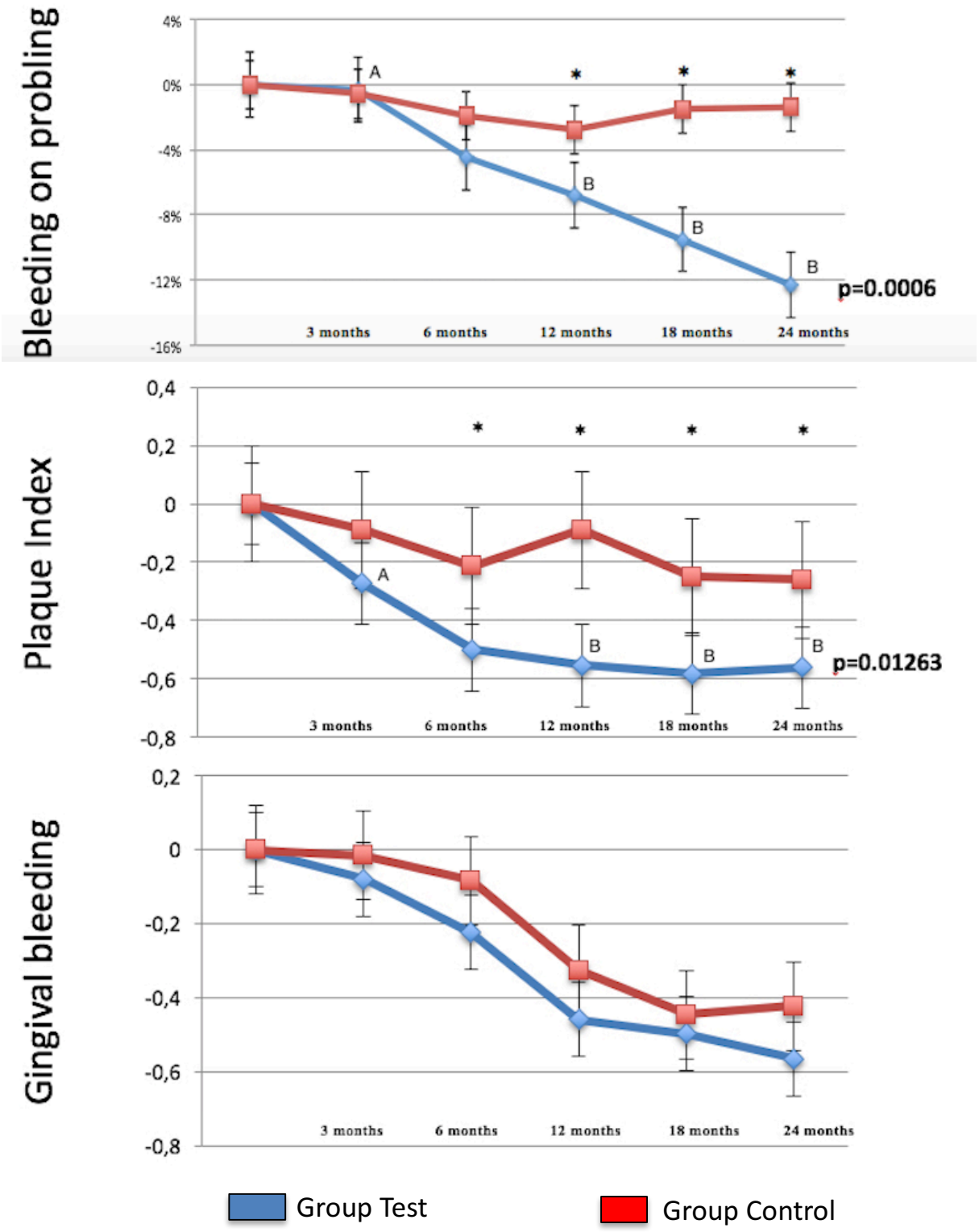
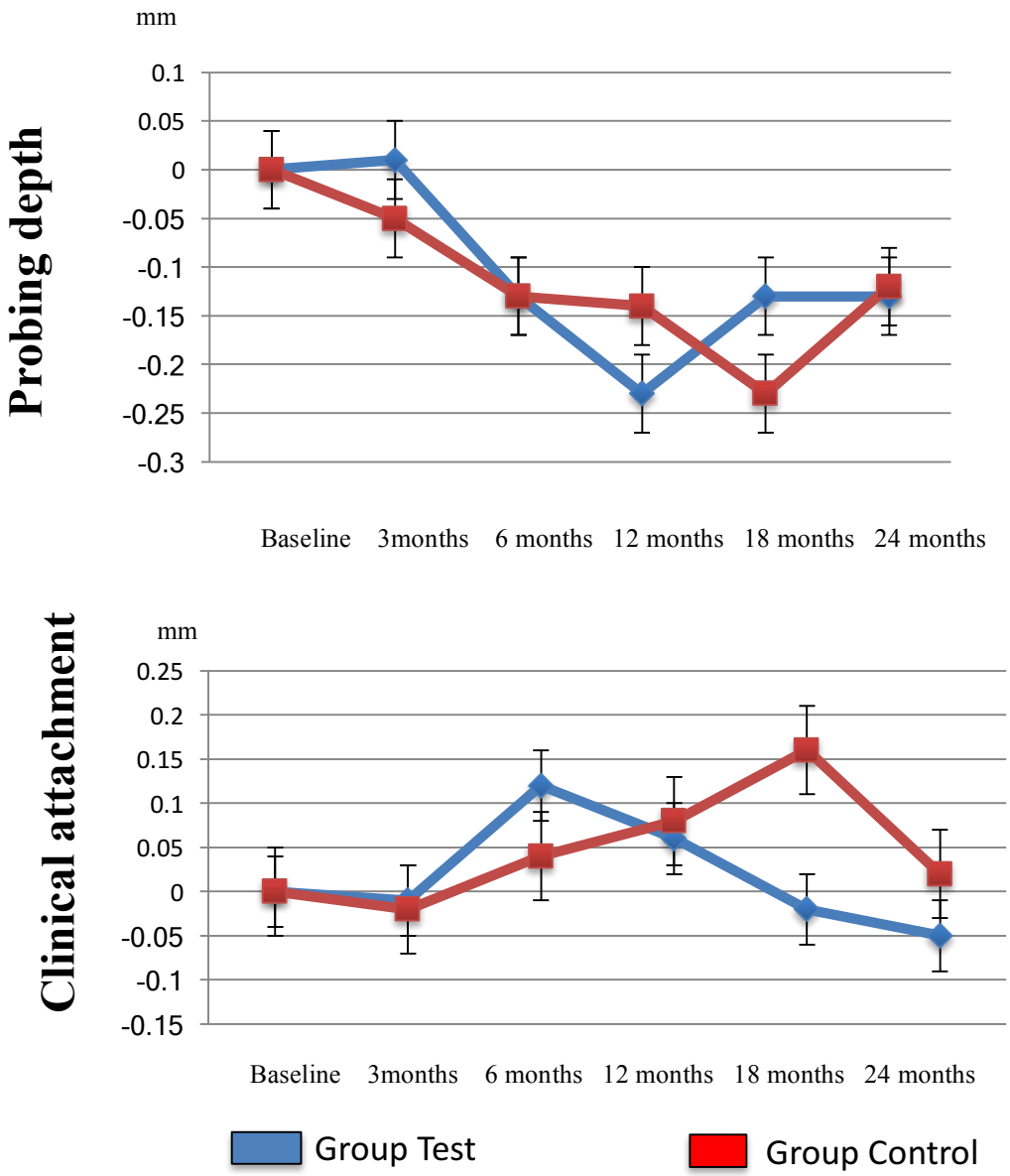


Figure 2.a. Line chart of mean changes in Bleeding on Probing, Plaque Index and Gingival Index between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* $p<0.05$).



Figuere 2.b. Line chart of mean changes in Probing Depth and Clinical Attachment between baseline and each follow-up time point. The test group is represented by the blue line and the control group by the red line. The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted to baseline mean values and treatment center (* $p<0.05$).

Table 2. Mean (± SEM) values for clinical parameters over the course of the study.

Variable	Time-point	Group		p-value
		Test	Control	
PI	Baseline	1.73 ± 0.13 [a]	1.60 ± 0.12	
	3 months	1.46 ± 0.13 [b]	1.48 ± 0.10	0.896
	6 months	1.23 ± 0.09 [b]	1.39 ± 0.10	0.288
	12 months	1.18 ± 0.11 [b]	1.51 ± 0.12	**0.049**
	18 months	1.12 ± 0.11 [c]	1.35 ± 0.10	0.142
	24 months	1.14 ± 0.10 [c]	1.34 ± 0.10	0.191
GI	Baseline	0.84 ± 0.12 [a]	0.87 ± 0.12 [a]	
	3 months	0.76 ± 0.13 [a]	0.86 ± 0.12 [a]	0.599
	6 months	0.62 ± 0.10 [b]	0.78 ± 0.12 [a]	0.311
	12 months	0.38 ± 0.07 [c]	0.54 ± 0.09 [b]	0.189
	18 months	0.38 ± 0.08 [c]	0.42 ± 0.08 [b]	0.738
	24 months	0.29 ± 0.05 [c]	0.45 ± 0.07 [b]	0.097
BOP (% of sites)	Baseline	19.0 ± 3.0 [a]	14.7 ± 2.1	
	3 months	18.7 ± 2.9 [a]	13.8 ± 14.1	0.160
	6 months	14.5 ± 2.7 [a]	12.8 ± 13.9	0.607
	12 months	12.2 ± 2.0 [b]	11.9 ± 12.4	0.916
	18 months	9.3 ± 1.6 [b]	13.3 ± 14.7	0.154
	24 months	6.6 ± 1.4 [c]	13.3 ± 15.2	**0.016**
PD (mm)	Baseline	1.94 ± 0.06	2.00 ± 0.06	
	3 months	1.95 ± 0.06	1.95 ± 0.05	0.990
	6 months	1.81 ± 0.05	1.87 ± 0.06	0.436
	12 months	1.71 ± 0.05	1.86 ± 0.06	0.068
	18 months	1.81 ± 0.05	1.77 ± 0.06	0.662
	24 months	1.81 ± 0.05	1.88 ± 0.06	0.439
CAL (mm)	Baseline	3.09 ± 0.14	3.13 ± 0.13	
	3 months	3.11 ± 0.15	3.14 ± 0.13	0.831
	6 months	2.98 ± 0.13	3.09 ± 0.13	0.575
	12 months	3.04 ± 0.15	3.05 ± 0.13	0.990
	18 months	3.12 ± 0.15	2.97 ± 0.14	0.478
	24 months	3.15 ± 0.14	3.11 ± 0.13	0.845

The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted for baseline mean values and treatment center.

SEM*:* standard errors of the mean*;* PI: plaque index; GI: gingival index; BOP: bleeding on probing; PD: probing depth; CAL: clinical attachment level; %: percentage

Table 3. Mean (± SEM) values for probing depth (PD) over the course of the study**.**

Variable	Time-point	Groups		p-value
		Test	Control	
PD≥5mm	Baseline	1.31 ± 2.15[A]	1.50 ± 4.76	0.816
	3 months	1.10 ± 2.10 [A]	1.29 ± 3.42	0.780
	6 months	0.56 ± 1.25 [B]	0.85 ± 2.40	0.496
	12 months	0.44 ± 0.88 [B]	0.96 ± 2.23	0.172
	18 months	0.52 ± 1.63 [B]	0.60 ± 1.73	0.827
	24 months	0.50 ± 1.18 [B]	0.60 ± 1.85	0.759
PD≥6mm	Baseline	0.49 ± 1.14	0.69 ± 2.82	0.678
	3 months	0.41 ± 1.07	0.49 ± 1.42	0.772
	6 months	0.13 ± 0.41	0.46 ± 1.72	0.246
	12 months	0.20 ± 0.61	0.44 ± 1.32	0.314
	18 months	0.22 ± 0.80	0.21 ± 0.82	0.990
	24 months	0.12 ± 0.33	0.33 ± 1.28	0.319
PD≥7mm	Baseline	0.20 ± 0.69	0.37 ± 1.90	0.597
	3 months	0.15 ± 0.49	0.29 ± 1.22	0.529
	6 months	0.05 ± 0.22	0.23 ± 0.99	0.277
	12 months	0.05 ± 0.32	0.21 ± 0.98	0.334
	18 months	0.07 ± 0.35	0.19 ± 0.73	0.377
	24 months	0.02 ± 0.16	0.12 ± 0.61	0.313

The significance of differences within each group over time was assessed by Repeated measures ANOVA and Tukey's multiple comparison tests (different letters represent $p<0.05$), and between the two groups at each time point by ANCOVA adjusted for baseline mean values and treatment center.

SEM*:* standard errors of the mean.

Table 4. Clinical relevance assessment for the effects of different toothpastes on "mea reduction in the percentage of sites with bleeding on probing from baseline to 24 months".

Outcome	Mean difference	Pooled SD	Effect size (ES)	Interpretation of ES	MID (0.2) = 0.2 x pooled SD	MID (0.5) = 0.5 x pooled SD	Final decision clinical relevance
Test-Control	11.0%	12.9%	0.85	LES	2.6%	6.5%	CR

When both the ES≥0.4 and the mean difference between groups are higher than both MIDs, clinical relevance is scored as CR. If ES is moderate and one of the MIDs is accomplished, it is scored as PCR. If ES is small-moderate and one of the MIDs is accomplished, it is also scored as PCR. If ES is small and one of the MIDs is accomplished, it is scored as NCR. If both (ES and MID) are not accomplished, then it is scored as NCR. Effects sizes are described according to Cohen (1988) as follows: SES: 0.20 (0-0.39); MES: 0.50 (0.40-0.79); LES: ≥0.80.

ES: effect size, MID: minimal important difference, NCR: not clinically relevant, PCR: potentially clinically relevant, CR: clinically relevant, SES: small effect size, MES: moderate effect size, LES: large effect size.

4. CONCLUSÃO

Os dados do presente estudo mostraram que um dentifrício contendo 0,3% de triclosan foi mais eficaz do que um dentifrício regular fluoretado na manutenção da estabilidade clínica e de um perfil microbiano subgengival mais benéfico em implantes que foram tratados para peri-implantite em indivíduos que seguiram um programa regular de manutenção por 2 anos. Além disso, o dentifrício contendo 0,3% triclosan foi mais eficaz na manutenção de um ambiente mais saudável ao redor dos implantes sem histórico de peri-implantitis e dos dentes naturais.

REFERÊNCIAS

Archila L, He T, Winston JL, Biesbrock AR, McClanahan SF, Bartizek RD. Antigingivitis efficacy of a stabilized stannous fluoride/sodium hexametaphosphate dentifrice in subjects previously nonresponsive to a triclosan/copolymer dentifrice. Compend Contin Educ Dent. 2005;26(9 Suppl 1):12-18.

Behneke A, Behneke N, d'Hoedt B. Treatment of peri-implantitis defects with autogenous bone grafts: six-month to 3-year results of a prospective study in 17 patients. Int J Oral Maxillofac Implants. 2000;15(1):125-138.

Boneta AE, Aguilar MM, Romeu FL, Stewart B, DeVizio W, Proskin HM. Comparative investigation of the efficacy of triclosan/copolymer/sodium fluoride and stannous fluoride/sodium hexametaphosphate/zinc lactate dentifrices for the control of established supragingival plaque and gingivitis in a six-month clinical study. J Clin Dent. 2010;21(4):117-123.

Botushanov PI, Grigorov GI, Aleksandrov GA. A clinical study of a silicate toothpaste with extract from propolis. Folia Med (Plovdiv). 2001;43(1-2):28-30.

Costa X, Laguna E, Herrera D, Serrano J, Alonso B, Sanz M. Efficacy of a new mouth rinse formulation based on 0.07% cetylpyridinium chloride in the control of plaque and gingivitis: a 6-month randomized clinical trial. J Clin Periodontol. 2013;40(11):1007-1015.

Cullinan MP, Westerman B, Hamlet SM, Palmer JE, Faddy MJ, Seymour GJ. The effect of a triclosan-containing dentifrice on the progression of periodontal disease in an adult population. J Clin Periodontol 2003; 30; 414–419.

Cummins D, Creeth JE. Delivery of antiplaque agents from dentifrices, gels, and mouthwashes. J Dent Res. 1992;71(7):1439-1449.

Cumming BR, Löe H. Consistency of plaque distribution in individuals without special home care instruction. J Periodontal Res. 1973;8(2):94-100.

Cury JA, Tenuta LM. Evidence-based recommendation on toothpaste use. Braz Oral Res. 2014;28 Spec No:1-7.
de Andrade Meyer AC, de Mello Tera T, da Rocha JC, Jardini MA. Clinical and microbiological evaluation of the use of toothpaste containing 1% chlorhexidine and

the influence of motivation on oral hygiene in patients with motor deficiency. Spec Care Dentist. 2010;30(4):140-145.

Derks J, Schaller D, Hakansson J, Wennstrom JL, Tomasi C, Berglundh T. Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-implantitis. J Dent Res. 2016;95(1):43-49.

Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. J Clin Periodontol. 2015;42 Suppl 16:S158-71.

Ellwood RP, Worthington HV, Blinkhorn AS, Volpe AR, Davies RM. Effect of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents. J Clin Periodontol. 1998 May;25(5):363-7.

Ericsson I, Persson LG, Berglundh T, Edlund T, Lindhe J. The effect of antimicrobial therapy on peri-implantitis lesion. An experimental study in dog. Clin Oral Implants Res. 1996; 7:320-328.

Ferrari, Daniel Sanchez. Avaliação longitudinal do metronidazol associado a amoxicilina no tratamento das periimplantites. 2008. Dissertação (Mestrado em Odontologia, área de concentração em Periodontia) – Centro de Pós-Graduação, Pesquisa e Extensão, Universidade Guarulhos, Guarulhos, SP, 2008.

Fine DH, Furgang D, Bontá Y, DeVizio W, Volpe AR, Reynolds H, Zambon JJ, Dunford RG. Efficacy of a triclosan/NaF dentifrice in the control of plaque and gingivitis and concurrent oral microflora monitoring. Am J Dent. 1998;11(6):259-270.

Gaffar A, Scherl D, Afflitto J. Coleman EJ. The effect of triclosan on mediators of gingival infiammation. J Clin Periodontoi 1995; 22: 480-484.

Hämmerle CHF, Fourmousis I, Winkler JR, Weigel C, Bragger U, Lang N.P. Successful bone fill in late peri-implant defects using guided tissue regeneration. A short communication. J Periodontol. 1995;66:303-308.

Haraszthy VI, Zambon JJ, Sreenivasan PK. Evaluation of the antimicrobial activity of dentifrices on human oral bacteria. J Clin Dent. 2010;21(4):96-100.

Hass R, Baron M, Dortbudak O, Watzek G. Lethal photosensitization, autogenous bone, and e-PTFE membrane for the treatment of peri-implantitis: preliminary results. Int J Oral Maxillof Implants. 2000;15:374-382.

Heitz-Mayfield LJ, Mombelli A. The therapy of peri-implantitis: a systematic review. Int J Oral Maxillofac Implants. 2014;29 Suppl:325-45.

Jenkins S, Addy M, Newcombe R. The effects of a chlorhexidine toothpaste on the development of plaque, gingivitis and tooth staining. J Clin Periodontol. 1993;20(1):59-62.

Kang JH, Jang YJ, Kim DJ, Park JW. Antimicrobial effectiveness of cetylpyridinium chloride and zinc chloride-containing mouthrinses on bacteria of halitosis and peri-implant disease. Int J Oral Maxillofac Implants. 2015;30(6):1341-1347.

Kerdvongbundit V, Wikesjö UM. Effect of triclosan on healing following non-surgical periodontal therapy in smokers. J Clin Periodontol. 2003 Dec;30(12):1024-30.

Khoury F, Buchmann R. Surgical therapy of peri-implant disease: a 3-year follow-up study of cases treated with 3 different techniques of bone regeneration. J Periodontol. 2001;72:1498-1508.

Kivela-Rajamaki MJ, Teronen OP, Maisi P, Husa V, Tervahartiala TI, Pirila EM, Salo TA, Mellanen L, Sorsa TA. Laminin-5 gamma2-chain and collagenase-2(MMP-8) in human peri-implant sulcular fluid. Clin Oral Implants Res. 2003;14:158-165.

Kjaerheim V, Skaare A, Barkvoll P, Rölla G. Antiplaque, antibacterial, and anti-inflammatory properties of triclosan mouthrinses in combination with zinc citrate or polyvinylmethylether maleic acid (PVM-MA) copolymer. Eur J Oral Sci. 1996;104(5-6):529-534.

Klinge B, Gustafsson A, Berglundh T. A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. J Clin Periodontol. 2002;29(suppl.3):213-225.

Lindhe J, Meyle J. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol. 2008;35 (Suppl. 8):282–285.

Mankodi S, Chaknis P, Panagakos FS, DeVizio W, Proskin HM. Comparative investigation of a dentifrice containing triclosan/copolymer/sodium fluoride and specially-designed silica and a dentifrice containing 0.243% sodium fluoride in a silica base for the control of established supra-gingival plaque and gingivitis: a 6-month clinical study. Am J Dent. 2011;24 Spec No A:21A-27A.

Mateu FA, Boneta AE, DeVizio W, Stewart B, Proskin HM. A clinical investigation of the efficacy of two dentifrices for controlling established supragingival plaque and gingivitis. J Clin Dent. 2008;19(3):85-94.

Modeer T, Bengtsson A, Rolla G. Triclosan reduces prostaglandin biosynthesis in human gingival fibroblasts challenged with interleukin-1 in vitro. J Clin Periodontol 1996; 23, 927-933.

Mombelli A. Prevention and therapy of peri-implant infections. In: Lang NP, Karring T, Lindhe J, ed. Proceedings of the 3rd European Worshop on Periodontology. Berlin: Quintessenz Verlag, 281-303, 1999.

Mombelli A, Feloutzis A, Brägger U, Lang NP. Treatment of peri-implantitis by local delivery of tretracycline: clinical, microbiological and radiological results. Clin Oral Implants Res. 2001;12:287-294.

Mombelli A, Lang NP. The diagnosis and treatment of peri-implantitis. Periodontol 2000. 1998;17:63-67.

Mombelli A, Muller N, Cionca N. The epidemiology of peri-implantitis. Clin Oral Implants Res. 2012; 23 Suppl 6:67-76.

Moran J, Addy M, Newcombe R. Comparison of an herbal toothpaste with a fluoride toothpaste on plaque and gingivitis. Clin Prev Dent. 1991;13(3):12-15.

Müller HP, Barrieshi-Nusair KM, Könönen E, Yang M. Effect of triclosan/copolymer-containing toothpaste on the association between plaque and gingival bleeding: a randomized controlled clinical trial. J Clin Periodontol. 2006;33(11):811-818.

Panagakos FS, Volpe AR, Petrone ME, DeVizio W, Davies RM, Proskin HM. Advanced oral antibacterial/anti-inflammatory technology: A comprehensive review of the clinical benefits of a triclosan/copolymer/fluoride dentifrice. J Clin Dent. 2005;16 Suppl:S1-19.

Pérez-Chaparro PJ, Duarte PM, Shibli JA, Montenegro S, Lacerda Heluy S, Figueiredo LC, Faveri M, Feres M. The Current Weight of Evidence of the Microbiologic Profile Associated With Peri-Implantitis: A Systematic Review. J Periodontol. 2016;87(11):1295-1304.

Pradeep AR, Agarwal E, Naik SB. Clinical and microbiologic effects of commercially available dentifrice containing aloe vera: a randomized controlled clinical trial. J Periodontol. 2012;83(6):797-804.

Ramanauskaite A, Juodzbalys G. Diagnostic Principles of Peri-Implantitis: a Systematic Review and Guidelines for Peri-Implantitis Diagnosis Proposal. J Oral Maxillofac Res. 2016 Sep 9;7(3):e8.

Ramberg P, Lindhe J, Botticelli D, Botticelli A. The effect of a triclosan dentifrice on mucositis in subjects with dental implants: a six-month clinical study. J Clin Dent. 2009;20(3):103-107.

Riley P, Lamont T. Triclosan/copolymer containing toothpastes for oral health. Cochrane Database Syst Rev. 2013;(12):CD010514.

Romeo E, Ghisolfi M, Murgolo N, Chiapasco M, Lops D, Vogel G. Therapy of peri-implantitis with resective surgery. A 3-year clinical trial on rough screw-shaped oral implants. Part I: clinical outcome. Clin Oral Implants Res. 2004;16:9-18.

Roos-Jansaker AM, Renvert S, Egelberg J. Treatment of peri-implant infections: a literature review. J Clin Periodontol. 2003;30:467-485.

Roos-Jansaker AM, Renvert H, Lindahl C, Rebvert S. Surgical treatment of peri-implantitis using a bone substitute with or without a resorbable membrane: a prospective cohort study. J Clin Periodontol. 2007;34:625-632.

Rosling B, Wannfors B, Volpe AR, Furuichi Y, Ramberg P, Lindhe J. The use of a triclosan/copolymer dentifrice may retard the progression of periodontitis. J Clin Periodontol. 1997;24(12):873-880.

Salvi GE, Cosgarea R, Sculean A. Prevalence and Mechanisms of Peri-implant Diseases. J Dent Res. 2017;96(1):31-37.

Schou S, Holmstrup P, Jørgensen T, Skovgaard LT, Stolze K, Hjørting-Hansen E, Wenzel A. Implant surface preparation in the surgical treatment of experimental peri-implantitis with autogenous bone graft and ePTFE membrane in cynomolgus monkeys. Clin Oral Implants Res. 2003;14:412-422.

Schwarz F, Sculean A, Rothamel D, Schwenzer K, Georg T, Becker J. Clinical evaluation of an Er:YAG laser for nonsurgical treatment of peri-implantitis: a pilot study. Clin Oral Implants Res. 2005;16:44-52.

Shibli JA, Martins MC, Theodoro LH, Lotufo RFM, Garcia VG, Marcantonio Jr. E. Lethal photosensitization in microbiological treatment of peri-implantitis: a preliminary study in dogs. J Oral Science. 2003;45:17-23.

Shibli JA, Martins MC, Ribeiro FS, Nociti Jr. FH, Garcia VG, Marcantonio Jr. E. Lethal photosensitization and guided bone regeneration in treatment of peri-implantitis. An experimental study in dogs. Clin Oral Implants Res. 2006;17:273-281.

Sreenivasan PK, Vered Y, Zini A, Mann J, Kolog H, Steinberg D, Zambon JJ, Haraszthy VI, da Silva MP, De Vizio W. A 6-month study of the effects of 0.3% triclosan/copolymer dentifrice on dental implants. J Clin Periodontol.2011;38:33–42.

Tonetti MS, Eickholz P, Loos BG, Papapanou P, van der Velden U, Armitage G, Bouchard P, Deinzer R, Dietrich T, Hughes F, Kocher T, Lang NP, Lopez R, Needleman I, Newton T, Nibali L, Pretzl B, Ramseier C, Sanz-Sanchez I, Schlagenhauf U, Suvan JE. Principles in prevention of periodontal diseases: Consensus report of group 1 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. J Clin Periodontol. 2015 Apr;42 Suppl 16:S5-11.

Triratana T, Kraivaphan P, Amornchat C, Mateo LR, Morrison BM Jr, Dibart S, Zhang YP. Comparing three toothpastes in controlling plaque and gingivitis: A 6-month clinical study. Am J Dent. 2015;28(2):68-74.

van der Ouderaa FJ. Anti-plaque agents. Rationale and prospects for prevention of gingivitis and periodontal disease. J Clin Periodontol. 1991;18(6):447-454.

Wilson TG Jr. Compliance. A review of the literature with possible applications to periodontics. J Periodontol. 1987;58(10):706-714.

Xu T, Deshmukh M, Barnes VM, Trivedi HM, Du-Thumm L, Richter R, Cummins D. Analysis of the antibacterial activity and plaque control benefit of colgate total dentifrice via clinical evaluation and real-time polymerase chain reaction. J Clin Dent.2005;16(4):117-122.

Yates R, Jenkins S, Newcombe R, Wade W, Moran J, Addy M. A 6-month home usage trial of a 1% chlorhexidine toothpaste (1). Effects on plaque, gingivitis, calculus and toothstaining. J Clin Periodontol.1993;20(2):130-138.

Zitzmann NU, Berglundh T. Definition and prevalence of peri-implant diseases. J Clin Periodontol. 2008 Sep;35(8 Suppl):286-291.