UNIVERSIDADE FEDERAL DE PELOTAS
Faculdade de Odontologia
Programa de Pós-Graduação em Odontologia

Dissertação de Mestrado

Terapias locais como adjuvantes a raspagem e alisamento radicular no tratamento periodontal não cirúrgico da periodontite agressiva: uma revisão sistemática.

Edvin Walter Brito Gomes

Pelotas, 2019

Edvin Walter Brito Gomes

Terapias locais como adjuvantes a raspagem e alisamento radicular no tratamento periodontal não cirúrgico da periodontite agressiva: uma revisão sistemática.

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Pelotas, como requisito parcial à obtenção do título de Mestre em Clínica Odontológica com ênfase em Periodontia.

Orientadora: Profa. Dra. Adriana Fernandes da Silva

Pelotas, 2019

Universidade Federal de Pelotas / Sistema de Bibliotecas
Catalogação na Publicação

G633t Gomes, Edvin Walter Brito

Terapias locais como adjuvante a raspagem e alisamento radicular no tratamento da periodontite agressiva : uma revisão sistemática / Edvin Walter Brito Gomes ; Adriana Fernandes da Silva, orientadora ; Maísa Casarin, Thiago Marchi Martins, coorientadores. — Pelotas, 2019.

50 f.

Dissertação (Mestrado) — Programa de Pós-Graduação em Clínica Odontológica - ênfase em Periodontia, Odontologia, Universidade Federal de Pelotas, 2019.

1. Doença periodontal. 2. Periodontite agressiva. 3. Raspagem e alisamento radicular. 4. Irrigação subgengival. I. Silva, Adriana Fernandes da, orient. II. Casarin, Maísa, coorient. III. Martins, Thiago Marchi, coorient. IV. Título.

Black : D64

Elaborada por Fabiano Domingues Malheiro CRB: 10/1955

Edvin Walter Brito Gomes

Terapias locais como adjuvantes a raspagem e alisamento radicular no tratamento periodontal não cirúrgico da periodontite agressiva: uma revisão sistemática.

Dissertação aprovada, como requisito parcial, para obtenção do grau deMestre em Clínica Odontológica com ênfase em Periodontia, Programa de Pós-Graduação em Odontologia, Faculdade de Odontologia, Universidade Federal de Pelotas.

Data da Defesa: 27 de fevereiro de 2019

Banca examinadora:

.....

Profa. Dra.Adriana Fernandes da Silva (Orientadora)
Doutora em Odontologiacom ênfase em Biologia Buco-Dental (Histologia e Embriologia)/Universidade Estadual de Campinas, UNICAMP, Brasil.

.....

Profa. Dra.Natália Marcumini Pola (membro interno titular)
Doutora em Odontologia área de concentração periodontia/Universidade Estadual Paulista Júlio de Mesquita Filho, UNESP, Brasil.

.....

Prof. Dr.Fábio Garcia Lima (membro externo titular)
Doutor em Odontologia área de concentração Dentistica/ Universidade Federal de Pelotas, Brasil.

.....

Prof. Dr. Wellington Luiz de Oliveira da Rosa (membro interno suplente)
Doutor em Biomateriais e Biologia Oral com ênfase em Materiais Odontológicos/Universidade Federal de Pelotas, Brasil.

.....

Prof. Dr. Josué Martos (Membro externo suplente)
Doutor em investigação avançada em odontologia/Universidade de Granada, Espanha.

.....

Dedico este trabalho aos meus pais, minha irmã e todos que me apoiaram nessa caminhada.

Agradecimentos

À Universidade Federal de Pelotas e á Faculdade de Odontologia por me proporcionarem esta formação profissional.

Ao Programa de Pós-Graduação em Odontologia e a todos os professores.

Á professora **Adriana Fernandes da Silva**, minha orientadora, por ter me possibilitado a realização do mestrado sob sua orientação, oportunizando meu crescimento científico e humano.

Aos meus co-orientadores, professor **Dr. Thiago Marchi Martins** e á professora **Dra. Maísa Casarin** por todo o apoio e suporte durante esta etapa.

A todos os colegas do PPGO, pela amizade e convivência e principalmente aos companheiros da área de concentração em clínica odontológica, pelos materiais emprestados e/ou doadosepelasexperiênciascompartilhadas.

ÀminhafamíliadePelotas, Gabriel, Lucas, Carlo, por compreenderem todos os momentos que deixei de participar das junções por conta do mestrado.

A todos que de alguma forma contribuíram para a realização deste trabalho.

Resumo

Gomes, Edvin Walter Brito. **Terapias locais como adjuvantes a raspagem e alisamento radicular no tratamento periodontal não cirúrgico da periodontite agressiva: uma revisão sistemática.** 2019. 52p. Dissertação de Mestrado- Programa de Pós-graduação em Odontologia, Faculdade de Odontologia, Universidade Federal de Pelotas, Pelotas, 2019.

Objetivo: Atualmente a raspagem e o alisamento radicular é o tratamento padrão inicial das doenças periodontais. O uso de terapias locais tem sido considerado como adjuvante no tratamento e na prevenção dessas condições. O objetivo deste trabalho foi realizar uma revisão sistemática sobre a efetividade de terapias locais como adjuvantes ao tratamento periodontal não cirúrgico da periodontite agressiva.

Materiais e Métodos: Sete bases de dados: Pubmed (Medline), Lilacs, Web ofScience, BBO, Scopus, SciELO e TheCochraneLibrary foram pesquisadas até agosto de 2018. Ensaios clínicos randomizadosque usaram terapias de liberação local como adjuvantes a raspagem e alisamento radicular em pacientes com periodontite agressiva com um período de acompanhamento maior que um mês foram incluídos no estudo. Profundidade de sondagem, nível de inserção clínica, indice de placa, inflamação gengival e sangramento á sondagem foram avaliados nos estudos incluídos.

Resultados: Um total de 2942 estudos foram encontrados, mas apenas 6 preencheram todos os critérios de seleção e foram incluídos na análise qualitativa. Simvastatin 1,2 mg e Alendronato 10mg/ml gel foram as substancias que apresentaram um melhor benefícios quando comparados com o grupo controle. Enquanto que substancias comoa clorexidina 1%, metronidazol gel 25%, doxiciclina gel 10%, tetraciclina 40% não apresentaram melhorias quandocomparadas com o grupo controle. Os estudos incluídos apresentaram heterogenidade metodológica, utilizaram diferentes substancias irrigadoras, protocolose formas de aplicação.

Conclusão: Embora a análise geral dessa revisão tenha mostrado os benefícios das terapias de liberação local para Alendronato e Simvastatin gel como adjuvante ao tratamento não cirurgíco da periodontite agressiva, mas devido a evidências insuficientes, não foi possivel comprovar as vantagens/benefícios da eficácia da terapia local como adjuvante ao tratamento padrão da periodontite agressiva. São necessários mais estudos clínicos randomizados bem delineados para confirmar a eficácia dessa terapia.

Palavras chaves: Doença periodontal, Periodontite agressiva, Raspagem e alisamento radicular, Irrigação subgengival.

Abstract

Gomes, Edvin Walter Brito, **Local therapies as adjuvant to scaling and root planning in non-surgical periodontal treatment of the aggressive periodontitis: a systematic review.** 2019, 52p. Masters Dissertation-Postgraduate Program in Dentistry.Federal University of Pelotas, Pelotas, 2019.

Aim: Scaling and root planing is currently the standard initial treatment of periodontal diseases. Local therapies been used as an adjuvant in the treatment and preventive therapy of periodontitis. The aim of this review is identifying if local therapy as an adjuvant to scaling and root planing lead to improvements in the periodontal clinical parameters in patients with aggressive periodontitis.

Materials and Methods: Seven databases: Pubmed (Medline), Lilacs, Web of Science, BBO, Scopus, SciELO and The Cochrane Library were searched up to until August of 2018. Randomized clinical trials using local delivery systems as an adjunct to scaling and root planing in patients with aggressive periodontitis with a follow-up period of more than one month were included in the study.

Results: A total of 2942 studies were found, but only 6 met all the selection criteria and were included in the qualitative analysis. Simvastatin 1.2 mg and Alendronate 10mg / ml gel were the substances that presented better benefits when compared with the control group. While substances such as 1% chlorhexidine, 25% metronidazole gel, 10% doxycycline gel, 40% tetracycline showed no improvement when compared to the control group. The studies showed a methodological heterogeneity, with different irrigating substances, protocols and forms of application used.

Conclusion: Although this review has shown the benefits of local release therapies for Alendronate and Simvastatin gel as an adjuvant to the non-surgical treatment of aggressive periodontitis, but due to insufficient evidence, it was not possible to prove the benefits / benefits of local therapy efficacy as adjuvant to the standard treatment of aggressive periodontitis. Further well-designed randomized clinical trials are required to confirm the efficacy of this therapy.

Key words: Periodontal diseases, Aggressive Periodontitis, Periodontal nonsurgicaltreatment, Scaling and root planning, Therapeutic irrigation.

LISTA DE FIGURAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

AgP	Aggressive periodontitis
SRP	Scaling and root planning
PD	Probing depth
CAL	Clinical attachment level
RCT	Randomized controlled trial
DP	Dental plaque
GI	Gingival inflammation
PB	Probing bleeding
ALN	Alendronate
IL	Interleukin
SMV	Simvastatin
BI	Bleeding Index
PI	Plaque index
mSBI	Modified sulcus bleeding index
SD	Standard deviation
MC	Maísa Casarin
AFS	Adriana Fernandes da Silva
EG	Edvin Gomes
TTC	Tetracycline
CHX	Chlorhexidine
MTZ	Metronidazole

Notas Preliminares

A presente dissertação foi redigida segundo o Manual de Normas para trabalhos acadêmicos da Universidade Federal de Pelotas, adotando o Nível de descrição em capítulos não convencionais. Disponível no endereço eletrônico: http://sisbi.ufpel.edu.br/arquivos/PDF/Manual_Normas_UFPel_trabalhos_acad%C3%AAmicos.pdf

O projeto de pesquisa que deu origem a esta dissertação foi apresentado na defesa de qualificação realizada em 29 de setembro de 2017 e aprovado pela Banca Examinadora composta pelos Professores: Doutora Adriana Fernandes da Silva, Doutora Noéli Boscato e Doutor Josué Martos.

Sumário

.

1 INTRODUÇÃO

As doenças periodontais consistem em processos inflamatórios de origem infecciosa que acometem os tecidos gengivais, chamadas gengivites, e/ou os tecidos de suporte dos dentes, chamadas periodontites (Vieira et al., 2010). São consequências das reações inflamatórias e imunológicas nos tecidos periodontais induzidas pelos micro-organismos da placa bacteriana, danificando o tecido conjuntivo e o osso alveolar (Slots, 2002). A gengivite é um achado universal na América Latina, afetando todas as idades, independentemente do nível socioeconômico. A extensão da presença de sangramento pode variar entre 40% e 70% dos sítios (Oppermann, 2007). A prevalência de periodontite crônica é alta e pode variar de 40% a 80%. enquanto que a prevalência de periodontite agressiva varia de 0,3% a 4,5%, sendo que a forma localizada é a menos prevalente (Oppermann, 2007). Essa variação pode ser explicada pelas diferenças na metodologia utilizada, diversos metodos de coleta de exames clínicos periodontais, tamanho da amostra, diferenças ambientais e culturais bem como a caracterização da faixa etária dos grupos estudados (Cortelliet al., 2002).

De acordo com a nova classificação das doenças periodontais (Catton, 2018), três formas de periodontites podem ser identificadas: periodontites necrotizantes, periodontites como forma de manifestação de doenças sistémicas e as formas antes conhecidas como crônica e agressiva que agora fazem parte de uma ùnica categoria chamada de periodontites. Segundo essa mesma classificação, as formas antes conhecidas como crônica e agressiva têm a mesma fisiopatologia, tendo alguns fatores relacionados ao individuo que podem modificar os desfechos dessa doença, como por exemplo, a resposta imune do hospedeiro que pode alterar o estabelecimento e a progressão da doença (Tonettiet al., 2018).

O tratamento da periodontite agressiva, assim como a periodontite crônica, centrou-se em duas abordagens fundamentais, ou seja, instruções de higiene oral para controle da placa supragengival e raspagem e alisamento radicular para a redução e/ou eliminação do biofilme e consequentemente da microbiotapatogênica (American Academy of Periodontology, 2000). Infelizmente, a raspagem e o alisamento radicular têm algumas limitações,

como dificuldades em acessar bolsas mais profundas, áreas de furca, concavidades radiculares (Badersten et al., 1987; Rabbani et al., 1981) e dificuldade de remover patógenos microbianos que são penetrados nos túbulos dentinários e que residem em lacunas e concavidades (Mombelli et al., 2011). Diante disso, a recolonização bacteriana da superfície radicular poderia levar à recidiva da doença após o tratamento (Cortelli et al., 2002).

Desta forma, terapias adjuntas com antibióticos sistêmicos têm sido amplamente utilizadas, especialmente em casos de periodontite agressiva. Porémo risco de desenvolver efeitos adversos, incluindo intolerância gastrointestinal e hipersensibilidade a antibióticos sistêmicos devem ser considerados e essa terapia deve ser limitado a pacientes com alto risco de progressão da doença periodontal (Flemmig et al., 1998). Assim, terapias locais podem ser uma alternativa muito interessante, especialmente em casos de rápida progressão, pois possuem a vantagem de liberar o fármaco no local de ação, possibilitando prolongar e/ou controlar sua concentração, reduzindo os riscos dos efeitos adversos e a possibilidade de resistência bacteriana apresentado pelo uso de antibioticos sistémicos (Brushi et al., 2006).

Neste sentido, terapias locais como gel de metronidazol, fibras de tetraciclina, chip de clorexidina, gel de doxiciclina entre outros tem sido amplamente utilizados nos dias de hoje, no entanto, essas terapias possuem algumas desvantagens que podem limitar ou até mesmo inviabilizar o seu emprego como: dificuldade em posicionar o agente dentro da bolsa e em lesões de furca, remoção do agente de dentro bolsa por parte do fluído crevicular gengival e limitação por uma única exposição e tempo de aplicação (Rams e Slots, 1996).

Na literatura não há revisão avaliando a eficácia das terapias locais em pacientes portadores de periodontite agressiva. Diante disso, o objetivo desta revisão é identificar se a terapia local como adjuvante à raspagem e alisamento radicular leva a melhorias nos parâmetros clínicos periodontais em pacientes com periodontite agressiva. A hipótese conceitual é que a terapia local como adjuvante à raspagem e alisamento pode levar a melhorias nos parâmetros clínicos periodontais em casos de periodontite agressiva quando comparada a raspagem e alisamento isolado ou a raspagem e alisamento combinado com um placebo.

2OBJETIVOS

2.1Geral

Avaliar sistematicamente se a terapia local como adjuvante à raspagem e alisamento radicular leva a melhorias nos parâmetros clínicos periodontais em pacientes com periodontite agressiva.

2.2 Específicos

2.2.1 Avaliar as mudanças na profundidade de sondagem e nível de inserção clinica após a terapia com sistemas de liberação local como adjuvante a raspagem e alisamento radicular em pacientes com periodontite agressiva.

2.2.2 Avaliar as mudanças no índice de placa, sangramento gengival e sangramento á sondagem após a terapia com sistemas de liberação local como adjuvante a raspagem e alisamento radicular em pacientes com periodontite agressiva.

3 HIPÓTESE

3.1 Terapias locais como adjuvante à raspagem e alisamento radicular mostram melhores parâmetros clínicos periodontais em casos de periodontite agressiva quando comparada a raspagem e alisamento radicular.

4 CAPÍTULO 1

LOCAL THERAPIES AS ADJUNVANTS TO SCALING AND ROOT PLANNING IN NON-SURGICAL PERIODONTAL TREATMENT OF THE AGGRESSIVE PERIODONTITIS: A SYSTEMATIC REVIEW

Edvin Walter Brito Gomes[1]
Maísa Casarin[2]
Thiago Marchi Martins[2]
Adriana Fernandes da Silva[3]

[1]Postgraduate Program in Dentistry, Dental School, Federal University of Pelotas, Brazil.
[2]Departament of Semiology and Clinic, Federal University of Pelotas, Brazil.
[3]Department of Restorative Dentistry, Dental School, Federal University of Pelotas, Brazil

Corresponding author:
Adriana Fernandes da Silva, Faculty of Dentistry, Postgraduate Program in Dentistry, Federal University of Pelotas
Gonçalves Chaves *St.*, 457/504, Centro
Zip Code: 96015-560
Pelotas, Brazil
E-mail: adrisilvapiva@gmail.com

---

*Artigo estruturado segundo as normas do periódico J ClinPeriodontol

Abstract

Gomes, Edvin Walter Brito, **Local therapies as adjuvant to scaling and root planning in non-surgical periodontal treatment of the aggressive periodontitis: a systematic review.** 2019, 51p.Masters Dissertation-Postgraduate Program in Dentistry. Federal University of Pelotas, Pelotas, 2019.

Aim: Scaling and root planing is currently the standard initial treatment of periodontal diseases. Local therapies been used as an adjuvant in the treatment and preventive therapy of periodontitis. The aim of this review is identifying if local therapy as an adjuvant to scaling and root planing lead to improvements in the periodontal clinical parameters in patients with aggressive periodontitis.

Materials and Methods: Seven databases: Pubmed (Medline), Lilacs, Web of Science, BBO, Scopus, SciELO and The Cochrane Library were searched up to until August of 2018. Randomized clinical trials using local delivery systems as an adjunct to scaling and root planing in patients with aggressive periodontitis with a follow-up period of more than one month were included in the study.

Results: A total of 2942 studies were found, but only 6 met all the selection criteria and were included in the qualitative analysis. Simvastatin 1.2 mg and Alendronate 10mg / ml gel were the substances that presented better benefits when compared with the control group. While substances such as 1% chlorhexidine, 25% metronidazole gel, 10% doxycycline gel, 40% tetracycline showed no improvement when compared to the control group. The studies showed a methodological heterogeneity, with different irrigating substances, protocols and forms of application used.

Conclusion: Although this review has shown the benefits of local release therapies for Alendronate and Simvastatin gel as an adjuvant to the non-surgical treatment of aggressive periodontitis, but due to insufficient evidence, it was not possible to prove the benefits / benefits of local therapy efficacy as adjuvant to the standard treatment of aggressive periodontitis. Further well-designed randomized clinical trials are required to confirm the efficacy of this therapy.

Key words: Periodontal diseases, Aggressive Periodontitis, Periodontal nonsurgical treatment, Scaling and root planing, Therapeutic irrigation.

INTRODUCTION

Periodontal diseases consist in the inflammatory processes affecting soft tissue as gingivitis and /or hard tissue as periodontitis (Vieira et al., 2010). Inflammatory and immune reactions in the periodontal tissues are induced by the plaque microorganism, damaging the connective tissue and the alveolar bone (Slots, 2002). The prevalence of chronic periodontitis is between 40% to 80% while the prevalence of aggressive periodontitis (AgP) showed a variation from 0.3% to 4.5%, being a localized form a less prevalent (Oppermann, 2007). This results can be explained by differences in the method of selection, methods of collecting clinical data, sample size, environmental and cultural differences, as well as a characterization of the age group of the studied groups (Cortelli et al., 2002).

According to the classification of periodontal diseases (Catton, 2018), the three forms of periodontitis can be identified: necrotizing periodontitis, periodontitis as a form of manifestation of systemic diseases and previous forms such as chronic and aggressive now grouped a single category the periodontitis. In addition, there have been some years related that the chronic and aggressive forms of periodontitis have the same pathophysiology, with some factors related to the individual that can modify the outcomes, such as a host immune response that can change the disease and the progression of the disease.

The treatment of AgP, as well as chronic periodontitis, focused on two fundamental approaches, namely, oral hygiene instructions for supragingival plaque control and scaling and root planing (SRP) for the reduction and / or elimination of the biofilm and consequently of the microbiota pathogenic (American Academy of Periodontology, 2000). Unfortunately, SRP have some limitations, such as difficulties in accessing deeper pockets, furcation areas, root concavities (Badersten et al., 1987; Rabbani et al., 1981) and the difficulty of removing microbial pathogens that are penetrated into the dentinal tubules and which reside in gaps and concavities (Mombelli et al., 2011). Thus, bacterial recolonization of the root surface could lead to recurrence of the disease after treatment (Cortelli et al., 2002).

Adjuvant therapies with systemic antibiotics have been widely used, especially in cases of AgP. Therefore risk of developing adverse effects, including gastrointestinal intolerance and hypersensitivity to systemic antibiotics should be considered and such therapy should be limited to patients at high risk of progression of periodontal disease (Flemmig et al., 1998). Thus, local therapy can be a very interesting alternative, especially in cases of rapid progression, since they have the advantage of releasing the drug at the site of action, making it possible to prolong and / or control its concentration, reducing the risks of adverse effects and possibility of bacterial resistance presented by the use of systemic antibiotics (Brushi et al., 2006).

In this sense, local therapy such as metronidazole (MTZ) gel, chlorhexidine (CHX) gel and chip, doxycycline gel, tetracycline (TTC) fibers, among others have been widely used these days, however, these therapy have some drawbacks that may limit or even render unfeasible the its use as: difficulty in positioning the agent inside the pocket and in furcation lesions, removal of the agent from the pouch by the gingival fluid and limitation by a single exposure and time of application (Rams and Slots, 1996).

In the literature there is no review evaluating the efficacy of local therapy in patients with AgP. Therefore, the objective of this review is to identify whether local delivery therapy as an adjunct to SRP leads to improvements in periodontal clinical parameters in patients with aggressive periodontitis. The conceptual hypothesis is that local delivery therapy as an adjunct to SRP may lead to improvements in periodontal clinical parameters in cases of AgP when compared to SRP alone or SRP combined with a placebo.

MATERIALS AND METHODS

This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis- PRISMA Statement (Moher et al. 2009). The protocol was registered in the international database for systematic reviews PROSPERO (CRD42018092434). The research question was: Does the use of local delivery systems as an adjuvant to conventional

periodontal treatment lead to clinical evidence of periodontal healing in cases of aggressive periodontitis?

Search strategies

Seven databases: Pubmed (Medline), Lilacs, Web of Science, BBO, Scopus, SciELO and The Cochrane Library were searched up to until August of 2018. The search developed for PubMed (Medline) and adapted for use in other databases is described in the appendix (Table 1). The references of the articles included were also manually checked. Duplicates were removed in Endnote X7 software (Thompson Reuters, Philadelphia, PA, USA).

Study selection

Two researchers selected the studies (EG and MC) independently using the abovementioned criteria. Third research was involved only in case of discrepancies (AFS). A hand search was performed in the references of every selected study. During the reading of title/abstract, the agreement between the researchers results in a kappa index = 0.78, and the agreement during the full-text results in a kappa index = 0.81.

Full-texts of all the potentially relevant studies were identified. Studies that appeared to meet the inclusion criteria or that there were insufficient data in the title and abstract to make a clear decision were selected for full analysis.

The inclusion criteria were: a) Randomized clinical trials with aggressive periodontitis patients; b) Use of localtherapy as an adjuvant to conventional periodontal treatment; c) Follow-up period of > 1 month; d) Studies with a negative control group (use of local therapy with serum or distilled water as adjuvant to the conventional periodontal treatment or only conventional periodontal).

The exclusion criteria were: a) Systematic reviews, review articles, in vitro studies, case series, case reports, case-control and other types of studies; b) Studies that used ultrasonic instruments and/or full mouth disinfection

therapy; c) Studies that used laser or photodynamic therapy; d) studies that used only systemic antibiotic treatment associated with periodontal treatment; e) studies that used local delivery systems adjuvant to periodontal treatment associated with systemic antibiotic therapy;

Clinical variables

The primary outcomes of interest were Clinical attachment level (CAL) gain andProbing depth (PD) reduction. CAL gain was defined as the difference between the CAL level measurements at baseline and final evaluation in each study. Likewise, PD reduction was defined as the difference between the baseline and last recordings. Dental plaque index (DP), gingival inflammation (GI) and probing bleeding (PB) were also analyzed as outcome.

Data extraction

Data extraction was performed in a spreadsheet developed for the present study. Two researchers were involved in this process (EG and MC). Again, the third researcher was involved only in case of discrepancy (AFS).The following data were tabulated from all papers included using data extraction sheets: demographic data, study design, number of patients, gender, age, intervention, application protocol, control group and follow-up of included studies. Additionally CAL gain and PD reduction were analyzed. Moreover, secondary outcomes such as dental plaque (DP), gingival inflammation (GI) and probing bleeding (PB) were also tabulated.

Assessment of Risk of Bias

The following criteria of publication bias from the RCT checklist of the Cochrane Center (Higgins JP, Green S, 2008) and the Consolidated Standards of Reporting Trials (CONSORT) statement were used: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel;

4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective outcome reporting; and 7) other sources of bias as sample calculation, and baseline balanced groups were analyzed.

The outcome assessment was categorized as follow: 1) low risk of bias if all key domains had low risk of bias; 2) high risk of bias if one key domain had risk of bias and 3) unclear risk of bias if onekey domain had one unclear risk of bias (Higgins JP, Green S, 2008).

RESULTS

The Figure 1 shows the flowchart that summarizes the article selection process according to the PRISMA Statement. Initially, 2492 potentially relevant records were identified from all databases. After examining the title and abstract, 1924 studies were excluded because they did not meet the selection criteria. Of the 47 studies retained for a detailed review and a total of 6 studies fulfilled all of the selection criteria and were included in the qualitative analysis.

Descriptive Analysis

All clinical trials included were published after 1995 (Table 2). Four studies used parallel designed (Yilmaz et al., 1996; Priyanka et al., 2017; Sharma et al., 2012; Unsal et al., 1995) and two split-mouths (Agan et al., 2006; Kadkhoda et al., 2012). A total of 84 subjects were evaluated with age between 16 and 50 years. One study had a maximum period of 42 days of follow-up (Yilmaz et al., 1996), two other studies used 90 days (Unsal et al., 1995; Kadkhoda et al., 2012) and three studies 180 days of follow-up (Priyanka et al., 2017; Sharma et al., 2012; Agan et al., 2006). SRP alone was the most treatment used as a control group (Unsal et al., 1995; Yilmaz et al., 1996; Kadkhoda et al., 2012; Agan et al., 2006) totalizing four studies. SRP with placebo gel was used intwo other studies (Priyanka et al., 2017; Sharma et al., 2012). Only two studies (Yilmaz et al., 1996; Kadkhoda et al., 2012) used the same drug (Elyzol®) as an intervention. One study used Alendronate (ALN),

(Priyanka et al., 2017) and other used simvastatin (SMV), (Sharma et al., 2012) as adjuvant to the periodontal treatment in the test group.

Methodological quality

Regarding the assessment of the risk of bias, Figure 2 summarizes the information used to assess the methodological quality of included studies. Only two studies described the method of randomization (Priyanka et al., 2017; Sharma et al., 2012), none described the allocation concealment and blindness of operators and evaluators. Two studies showed the sample calculation (Priyanka et al., 2017; Sharma et al., 2012) and only two didn't report a loss of participants at the time of follow- up (Sharma et al., 2012; Yilmaz et al., 1996).

Clinical outcomes

Dental plaque

There was a significant reduction in DP index in both intervention case and control groups. Unsal et al., 1995 showed that the use of 40% TTC Hydrochloride as an adjuvant to SRP had a reduction of dental plaque when compared to 1% CHX and control groups (table 3).

Gingival Inflammation and Probing bleeding

GI and PBdata are reported in table 3. There was a significant reduction in GI levels in all groups of the studies, except in the control group of one study (Priyanka et al., 2017).Besides there was a significant reduction of 94.52% in PB in the group that used MTZ gel 25% (Elyzol®) as adjuvant to SRP compared to the control group (Kadkhoda et al., 2012). (Table 3)

PD reduction and CAL gain

PD reduction and CAL gain data are reported in table 4. The mean of PD decreased in all groups, although with statistical differences favoring the intervention groups in only 3 studies (Priyanka et al., 2017, Sharma et al., 2012

and Yilmaz et al., 1996) that used 1.2 mg SMV gel, ALN gel (10 mg/mL) and 25% MTZ gel (Elyzol®) respectively. CAL gain was observed in all groups, but the statistical difference was no significant in 4 studies (Kadkhoda et al., 2012; Agan et al., 2006, Unsal et al., 1995 and Yilmaz et al., 1996) when compared intervention groups with control groups. The CAL gain was statistically significant in two studies (Sharma et al., 2012and Priyanka et al., 2017) when used 1.2 mg SMV gel and ALN gel (10 mg/mL).

DISCUSSION

This systematic review addressed the focused question**:** Does the use of local therapy as an adjuvant to non-surgical periodontal treatment lead to benefits in periodontal clinical parameters in cases of AgP? The findings of this study show that local therapies seem to promote an additional benefit to SRP in the treatment of AgP, but due to the low number of well-designed randomized clinical studies, it is not possible to make this statement, in this way our initial hypothesis was rejected.

Priyanka et al., 2017 showed that CAL gain was statistically significant in the group that used 1.2 mg of SMV gel when compared to the control group (SRP+ placebo gel). This can be explained because SMV decreases the production of interleukin (IL)-6 and -8, reduce nuclear factor-kappa B and activator protein 1 promoter human epithelial cell line indicating an anti-inflammatory effect (Sakoda et al., 2006). SMV exhibits a positive impact on the proliferation and osteoblastic differentiation of human periodontal ligament cells and this effect may be caused by inhibition mevalonate pathway (Priyanka et al., 2017). Besides SMV is reported to stimulate vascular endothelial grown factor in bone tissue, and this way it promotes the osteoblast differentiation, and the bone nodule formation (Henwood, 1988).

CAL gain was statistically significant in the group that used ALN gel (Sharma et al., 2012). The authors believe that the Bisphosphonate can inhibit the osteoclasts by inducing their apoptosis and also by reduce the hematopoietic activity to osteoclastprecursors, as well as it stimulates the

production of osteoclast inhibitory factor (Hughes 1995, Sato 1990, Vitté 1996). It has also beenshown that the ALN can causea rise in intracellular calciumlevels in an osteoclast-like cell line (Colucci, 1998). Bisphosphonate have been shown to inhibit osteoclast-mediated bone resorption to significantly increase bone mineral density (Hwang et al., 2010). Studies have demonstrated that topical application of ALN washighly effective in reducing alveolar bone resorption, can stimulate a significant PD reduction, CAL gain, and improved bonefill compared to placebo gel as an adjunct to SRP in the treatment of Chronic periodontitis (Yaffe et al., 1995; Sharma et al., 2012).

The results of two studies (Kadkhoda et al., 2012; Yilmaz et al., 1996) showed that SRP plus MTZ gel at 25% was superior to the conventional treatment of SRP alone regarding PD, PB, and CAL. Some studies (Arthur et al., 2005, Griffiths et al., 2000) showed similar results. Another substance used in the study of Unsal et al. 1995 was TTC. The results showed a decrease in PD means, but there was no significant difference when compared to the control group. TTC are primarily bacteriostatic antimicrobials, effective against all Gram-positive bacteria (Abdulpur, 1995), and many Gram-negative species. These drugs may have the anti-inflammatory effect because of their ability to block the activity of collagenolytic enzyme (Abdulpur, 1995) and this may explain the benefits of tetracycline in periodontal treatment.

All studies included in this review exhibited that the treatment different used to the AgP brought benefits in the clinical parameters. However, four studies (Kadkhoda et al., 2012; Agan et al., 2006, Unsal et al., 1995 and Yilmaz et al., 1996) didn't show statistical differences in CAL gain favoring the groups that used local therapies as an adjuvant to SRP in the treatment of AgP. Even today, SRP remains as the 'gold standard' to thesuccessful periodontal therapy, and can explain the benefits in the clinical parameters in all studies included in this review.

Due to the limitations of SRP, combined treatment with manual and mechanical instrumentation associated with the local therapy of antimicrobial agents has been investigated widely. Some studies showed that 10% Povidone-iodine irrigation as an adjunct to SRP favored the nonsurgical periodontal therapy in chronic periodontitis, due to its broad-spectrum antimicrobial activity (Denez et al., 2016; Sindhura et al., 2017). CHX 0.2% showed a significant

decline in periodontal inflammation and reduction in periodontopathogenic microflora in patients with chronic periodontitis when used as an adjunct to SRP (Albullais et al., 2015; Pandya et al., 2016). Recently a systematic review concluded that exist insufficient evidence supporting the efficacy of subgingival irrigation as an adjunct to SRP in treating of chronic periodontitis and if braiding of AgP becomes even more difficult, because it is a condition not very prevalent and with few studies well delineated.

Local therapy can be a very interesting alternative, especially in cases of rapid progression, because it makes it possible to release the drug at the site of action, making it possible to prolong and / or control its concentration, reducing the risks of adverse effects and possibility of bacterial resistance presented by the use of systemic antibiotics (Brushi et al., 2006). However, these therapies have some limitation, such as: difficulty in positioning the agent inside the pocket and in furcation lesions, removal of the agent from the pouch by the gingival fluid and limitation by a single exposure and time of application (Rams and Slots, 1996).

Although concepts of aggressive and chronic periodontitis no longer exist in the classification of periodontal diseases, now integrating the category of "periodontitis" (Papapanou 2018; Needleman, 2018) are conditions that can still be identified independently and characteristics similar to aggressive form can be found in the new classification independent of the age of the individual. Now periodontitis are classified based on a multidimensional staging and grading system that could be adapted over time as new evidence emerge (Tonetti et al. 2018).

In this review, we attempted to include all local delivery systems, but only studies using gel met the inclusion criteria. Studies with others local therapies such as chip, paste and other forms should be considered in future studies.

It is essential to consider the limitations of the evidence available, considering that the included studies didn't explicitly mention about randomization, allocation concealment, blinding, formulation of irrigants, type and formulation of placebo gel and severity of periodontal disease. The present systematic review found that the use of local delivery systems as an adjuvant to SRP may provide additional clinical benefits compared to SRP alone or with placebo. However, it would seem inappropriate to make definitive statements

regarding the efficacy of treatment modalities based on available information. Future well-designed RCTs should include large sample size, high methodological quality, and adverse event analysis to confirm these findings.

CONCLUSION

Although in the qualitative analysis a better result was shown for SMV and ALN gel, local therapies as adjuvant to SRP, the data found were limited due the heterogeneity among the studies. This way, upcoming clinical studies with appreciable methodological quality should be performed considerating the new classification.

REFERENCES

Abdulpur MS. Periodontal microbiology. J Indian Soc of Periodontol. 1995; 19(1):54–9.

Abullais SS, Dani N, Hamiduddin, Priyanka N, Kudyar N, Gore A, Efficacy of irrigation with different antimicrobial agents on periodontal health in patients treated for chronic periodontitis: A randomized controlled clinical trial, Ayu. 2015 Oct-Dec; 36(4):380-386.

Agan S, Sonmez S, Serdar M, The effect of topical doxycycline usage on gingival crevicular fluid MMP-8 levels of chronic and aggressive periodontitis patients: a pilot study, Int J Dent Hygiene4, 2006; 114–121.

Albandar JM, Brown LJ, Loe H. Putative periodontal pathogens in subgingival plaque of young adults with and without early-onset periodontitis. J Periodontol 1997; 68:973-981.

Albandar JM, Tinoco EM. Global epidemiology of periodontal diseases in children and young persons.Periodontol 2000 2002; 29:153-176.

Albandar JM. Juvenile periodontitis – pattern of progression and relationship to clinical periodontal parameters. Community Dent Oral Epidemiol 1993; 21:185-9.

American Academy of Periodontology. Parameter on aggressive periodontitis.J Periodontol2000; 71(Suppl.5):867-869.

Armitage GC. Development of a classification system for periodontal diseases and conditions.AnnPeriodontol 1999; 4:1-6.

Arthur J. Bonito, Linda Lux, and Kathleen N.Lohr. Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. J Periodontol 2005 Aug; 76(8):1227-36.

Badersten A, Nilveus R, Egelberg J. Effect of nonsurgical periodontal therapy (VIII). Probing attachment changes related to clinical characteristics. J Clin Periodontol.1987; 14(7):425-32.

Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, Mealey BL, Papapanou PN, Sanz M, Tonetti MS, A new classification scheme for periodontal and peri-implant diseases and conditions- introduction and key changes form 1999 classification, J periodontal. 2018 Jun; 89 Suppl 1: S1-S8. Doi: 10.1002/JPER.18-0157.

Cortelli JR, Cortelli SC, Pallos D, Jorge AOC, Prevalence of aggressive periodontitis in adolescents and young adults from Vale do Paraíba, PesquiOdontol Bras 2002;16(2):163-168.

Denez EM, Toma S, Lasserre JF, BrecxMC.Evaluation of a unique subgingival irrigation with 10% povidone-iodine after scaling and root planing: A randomized clinical trial, Quintessence Int. 2016;47(7):549-58.

Flemmig TF, Milián E, Karch H, Klaiber B. Differential clinical treatment outcome after systemic metronidazole and amoxicillin in patients harboring *Actinobacillusactinomycetemcomitans* and/or *Porphyromonasg ingivalis*. J ClinPeriodontol. 1998; 25:380–387.doi: 10.1111/j.1600-051X.1998.tb02459.x.

Griffiths GS, Smart GJ, Bulman JS, Weiss G. Shrowder J, Newman HN. Comparison of clinical outcomes following treatment of chronic adult periodontitis with subgingival scaling or subgingival scaling plus metronidazole gel. J ClinPeriodontol 2000 Dec; 27(12):910-17.

Hallmon WW, Rees TD. Local anti-infective therapy: Mechanical and physical approaches. A systematic review. Ann Periodontol. 2003; 8(1):99-114.

Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions: cochrane book series. Wiley: Hoboken.

Hughes A, Rogers MJ, Idris AL, Crockett JC.A comparison between the effects of hydrophobic and hydrophilic statines on osteoclast functions in vitro and ovariectomy-induced bone loss in vivo. Calcify tissue int 2007; 81:403-413.

Hwang JS, Liou MJ, Ho C, et al. The effects of weeklyAlendronate therapy in Taiwanese males with osteoporosis.J Bone Miner Metab2010; 28:328-333.

Kadkhoda Z, Rafiei Tari S, Owlia P, Seyyed Zadeh Sabounchei S, Comparison of 1-Periodontal Indices and Cultural PorphyromonasGingivalis Colony Count in Aggressive Periodontitis Patients Treated by Scaling and Root planning with or Without Metronidazole Gel. Journal of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (2012; Vol. 9, No.1).

Kinane DF, Hart TC. Genes and gene polymorphisms associated with periodontal disease. Crit Rev Oral Biol Med 2003; 14:430-449.

Klaus H, Rateitschak KH, Wolf HF, Hasseil TM. A Colour Atlas of Dental Medicine, 2nd ed. Stuttgart: Georg Theime Verlag; 1989; 41.

Löe H, Brown LJ. Early onset periodontitis in the United States of America.J Periodontol 1991; 62:608-16.

Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta OdontolScand 1963; 21:533-551.

Lopez NJ, Rios V, Pareja MA, Fernandez O. Prevalenceof juvenil periodontitis in Chile. J ClinPeriodontol 2001; 8:529-33.

Marcos Luciano Bruschi, Heitor Panzeri, Osvaldo de Freitas, Elza Helena Guimarães Lara, Maria Palmira DaflonGremião, Periodontal pocketdrug delivery systems, Ver. Bras. Cienc. Farm. Vol.42 no.1 São Paulo Jan./Mar.2006.

Meng H, Xu L, Li Q, Han J, Zhao Y. Determinantsof host susceptibility in aggressiveperiodontitis. Periodontol 2000 2007; 43:133-159.

Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62:1006–1012. Https: //doi.org/10.1016/j.jclin epi.2009.06.005.

Mombelli A, Cionca N, Almaghlouth A. Does adjunctive antimicrobial therapy reduce the perceived need for periodontal surgery? Periodontol 2000. 2011; 55(1):205-16.

Mombelli A, van Oosten MA, Schurch E, Lang NP. The microbiota associated with successful or failing osseointegrated titanium implants.OralMicrobiol Immunol1987; 2:145-151.

Nagarakanti S, Gunupati S, Chava VK, Reddy BV, Effectiveness of Subgingival Irrigation as an Adjunct to Scaling and Root Planing in the Treatment of Chronic Periodontitis: A Systematic Review, J Clin Diagn Res. 2015 Jul;9(7):ZE06-9.

Needleman I, Garcia R, Gkranias N, et al. Mean annual attachment, bone level and tooth loss: A systematic review. J ClinPeriodontol. 2018;45(Suppl 20):S112–S129.

Nibali L, Ready DR, Parkar M, et al. Gene polymorphisms and the prevalence of key periodontal pathogens.J Dent Res2007; 86:416-420.

Pandya DJ, Manohar B, Mathur LK, Shankarapillai R, Comparative evaluation of two subgingival irrigating solutions in the management of periodontal disease: A clinicomicrobial study, J Indian SocPeriodontol. 2016 Nov-Dec; 20(6):597-602.

Papapanou PN, Sanz M, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions. J ClinPeriodontol. 2018; 45(Suppl 20): S162–S170.

Priyanka N, Abhilash A, Saquib S, Malgaonkar N, Kudyar N, Gupta A, Kalra N, Pradeep AR. Clinical Efficacy of subgingivally delivered 1.2 mg simvastatin in the treatment of patients with Aggressive Periodontitis: A Randomized Controlled Clinical Trial. Int J PeriodonticsRestorativeDent. 2017 Mar/Apr; 37(2): e135-e141. Doi: 10.11607/prd.2936.

Rabbani GM, Ash MM, Caffesse RG. The effectiveness of subgingival scaling and root planing in calculus removal. J Periodontol. 1981; 52(3):119-23.

Sakoda K, Yamamoto M, Negishi y, Lyao JK, Node K, Izumi Y. Simvastatin decreases IL-6 and IL-8 production in epithelial cells. J Dent Res 2006; 85:520-523.

Saxen L. Juvenile periodontitis. JClinPeriodontol 1980; 7:1-19.

Sharma A, Pradeep A.R, Clinical Efficacy of 1% Alendronate Gel in Adjunct to Mechanotherapy in the J Periodontol Treatment of Aggressive Periodontitis: A Randomized Controlled Clinical Trial, the J Periodontol. 2012 Jan; 83(1):19-26. Doi: 10.1902/jop.2011.110206. Epub 2011 May 24.

Shiloah J, Hovious LA. The role of subgingival irrigations in the treatment of periodontitis. J Periodontol.1993; 64(9):835-43.

Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta OdontolScand 964; 22:121-123.

Sindhura H, Harsha RH, Shilpa RH, Efficacy of subgingival irrigation with 10% povidone-iodine as an adjunct to scaling and root planing: A clinical and microbiological study, Send toIndian J Dent Res. 2017 Sep-Oct;28(5):514-518.

Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J ClinPeriodontol. 2018; 45(Suppl 20):S149–S161

Ünsal E, Frank Walsh T, Akkaya M, The Effect of a Single Application of Subgingival Antimicrobial or Mechanical Therapy on the Clinical Parameters of Juvenile Periodontitis.J Periodontal January 1995; 66:47-51.

Yaffe A, Fine N, Alt I, Binderman I. Effect of bisphosphonate on alveolar bone resorption followingmucoperiosteal flap surgery in the mandible of rats.JPeriodontol1995; 66:999-1003.

Yilmaz S, Kuru B, Noyan U, Kadir T, Acar O, Buget E, A clinical and microbiological evaluation of systemic and local metronidazole delivery in early onset periodontitis patients, Journal of Marmara University Dental Faculty, Vol 2 n 2-3, September 1996.

VIEIRA, T. R. et al. Alterações periodontais associadas às doenças sistêmicas em crianças e adolescentes. Rev Paul Pediatr, v. 28, n. 2, p. 237-243, 2010.

Oppermann, Rui Vicente, An overview of the epidemiology of periodontal diseases in Latin America, Braz Oral Res 2007;21(Spec Iss 1):8-15.

Rams TE. Slots J. Local delivery of antimicrobial agents in the periodontal pocket. Periodontol 2000. 1996;10:139-159.

Solts J. Selection of antimicrobial agents in periodontal therapy. J Periodontal Res. 2002; 37:389-398.

5 CONCLUSÃO

Embora a análise geral dessa revisão tenha mostrado os benefícios dos sistemas de liberação local para Alendronato e Simvastatin gel como adjuvante ao SRP, os dados encontrados foram limitados devido à heterogeneidade dos estudos. Os estudos incluidos não foram claros quanto aos critérios de diagnostico da periodontite, randomização, cegamento, cálculo da amostra, protocolo de irrigação e formulação da substancias utilizadas. Desta forma,estudos clínicos com qualidade metodológica apreciável devem ser realizados considerando a nova classificação.

6 REFERÊNCIAS

Abdulpur MS. Periodontal microbiology. J Indian Soc of Periodontol. 1995; 19(1):54–9.

Abullais SS, Dani N, Hamiduddin, Priyanka N, Kudyar N, Gore A, Efficacy of irrigation with different antimicrobial agents on periodontal health in patients treated for chronic periodontitis: A randomized controlled clinical trial, Ayu. 2015 Oct-Dec; 36(4):380-386.

Agan S, Sonmez S, Serdar M, The effect of topical doxycycline usage on gingival crevicular fluid MMP-8 levels of chronic and aggressive periodontitis patients: a pilot study, Int J Dent Hygiene4, 2006; 114–121.

Albandar JM, Brown LJ, Loe H. Putative periodontal pathogens in subgingival plaque of young adults with and without early-onset periodontitis. J Periodontol 1997; 68:973-981.

Albandar JM, Tinoco EM. Global epidemiology of periodontal diseases in children and young persons.Periodontol 2000 2002; 29:153-176.

Albandar JM. Juvenile periodontitis – pattern of progression and relationship to clinical periodontal parameters. Community Dent Oral Epidemiol 1993; 21:185-9.

American Academy of Periodontology. Parameter on aggressive periodontitis.J Periodontol2000; 71(Suppl.5):867-869.

Armitage GC. Development of a classification system for periodontal diseases and conditions.AnnPeriodontol 1999; 4:1-6.

Arthur J. Bonito, Linda Lux, and Kathleen N.Lohr. Impact of local adjuncts to scaling and root planing in periodontal disease therapy: a systematic review. J Periodontol 2005 Aug; 76(8):1227-36.

Badersten A, Nilveus R, Egelberg J. Effect of nonsurgical periodontal therapy (VIII). Probing attachment changes related to clinical characteristics. J Clin Periodontol.1987; 14(7):425-32.

Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, Mealey BL, Papapanou PN, Sanz M, Tonetti MS, A new classification scheme for periodontal and peri-implant diseases and conditions- introduction and key changes form 1999 classification, J periodontal. 2018 Jun; 89 Suppl 1: S1-S8. Doi: 10.1002/JPER.18-0157.

Cortelli JR, Cortelli SC, Pallos D, Jorge AOC, Prevalence of aggressive periodontitis in adolescents and young adults from Vale do Paraíba, PesquiOdontol Bras 2002;16(2):163-168.

Denez EM, Toma S, Lasserre JF, BrecxMC. Evaluation of a unique subgingival irrigation with 10% povidone-iodine after scaling and root planing: A randomized clinical trial, Quintessence Int. 2016;47(7):549-58.

Flemmig TF, Milián E, Karch H, Klaiber B. Differential clinical treatment outcome after systemic metronidazole and amoxicillin in patients harboring *Actinobacillusactinomycetemcomitans* and/or *Porphyromonasg ingivalis*. J ClinPeriodontol. 1998; 25:380–387.doi: 10.1111/j.1600-051X.1998.tb02459.x.

Griffiths GS, Smart GJ, Bulman JS, Weiss G. Shrowder J, Newman HN. Comparison of clinical outcomes following treatment of chronic adult periodontitis with subgingival scaling or subgingival scaling plus metronidazole gel. J ClinPeriodontol 2000 Dec; 27(12):910-17.

Hallmon WW, Rees TD. Local anti-infective therapy: Mechanical and physical approaches. A systematic review. Ann Periodontol. 2003; 8(1):99-114.

Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions: cochrane book series. Wiley: Hoboken.

Hughes A, Rogers MJ, Idris AL, Crockett JC. A comparison between the effects of hydrophobic and hydrophilic statines on osteoclast functions in vitro and ovariectomy-induced bone loss in vivo. Calcify tissue int 2007; 81:403-413.

Hwang JS, Liou MJ, Ho C, et al. The effects of weekly Alendronate therapy in Taiwanese males with osteoporosis.J Bone Miner Metab2010; 28:328-333.

Kadkhoda Z, Rafiei Tari S, Owlia P, Seyyed Zadeh Sabounchei S, Comparison of 1-Periodontal Indices and Cultural Porphyromonas Gingivalis Colony Count in Aggressive Periodontitis Patients Treated by Scaling and Root planning with or Without Metronidazole Gel. Journal of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (2012; Vol. 9, No.1).

Kinane DF, Hart TC. Genes and gene polymorphisms associated with periodontal disease. Crit Rev Oral Biol Med 2003; 14:430-449.

Klaus H, Rateitschak KH, Wolf HF, Hasseil TM. A Colour Atlas of Dental Medicine, 2nd ed. Stuttgart: Georg Theime Verlag; 1989; 41.

Löe H, Brown LJ. Early onset periodontitis in the United States of America.J Periodontol 1991; 62:608-16.

Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. Acta OdontolScand 1963; 21:533-551.

Lopez NJ, Rios V, Pareja MA, Fernandez O. Prevalence of juvenil periodontitis in Chile. J ClinPeriodontol 2001; 8:529-33.

Marcos Luciano Bruschi, Heitor Panzeri, Osvaldo de Freitas, Elza Helena Guimarães Lara, Maria Palmira Daflon Gremião, Periodontal pocketdrug delivery systems, Ver. Bras. Cienc. Farm. Vol.42 no.1 São Paulo Jan./Mar.2006.

Meng H, Xu L, Li Q, Han J, Zhao Y. Determinants of host susceptibility in aggressive periodontitis. Periodontol 2000 2007; 43:133-159.

Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62:1006–1012. Https: //doi.org/10.1016/j.jclin epi.2009.06.005.

Mombelli A, Cionca N, Almaghlouth A. Does adjunctive antimicrobial therapy reduce the perceived need for periodontal surgery? Periodontol 2000. 2011; 55(1):205-16.

Mombelli A, van Oosten MA, Schurch E, Lang NP. The microbiota associated with successful or failing osseointegrated titanium implants.OralMicrobiol Immunol1987; 2:145-151.

Nagarakanti S, Gunupati S, Chava VK, Reddy BV, Effectiveness of Subgingival Irrigation as an Adjunct to Scaling and Root Planing in the Treatment of Chronic Periodontitis: A Systematic Review, J Clin Diagn Res. 2015 Jul;9(7):ZE06-9.

Needleman I, Garcia R, Gkranias N, et al. Mean annual attachment, bone level and tooth loss: A systematic review. J ClinPeriodontol. 2018;45(Suppl 20):S112–S129.

Nibali L, Ready DR, Parkar M, et al. Gene polymorphisms and the prevalence of key periodontal pathogens.J Dent Res2007; 86:416-420.

Pandya DJ, Manohar B, Mathur LK, Shankarapillai R, Comparative evaluation of two subgingival irrigating solutions in the management of

periodontal disease: A clinicomicrobial study, J Indian SocPeriodontol. 2016 Nov-Dec; 20(6):597-602.

Papapanou PN, Sanz M, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions. J ClinPeriodontol. 2018; 45(Suppl 20):S162–S170.

Priyanka N, Abhilash A, Saquib S, Malgaonkar N, Kudyar N, Gupta A, Kalra N, Pradeep AR. Clinical Efficacy of subgingivally delivered 1.2 mg simvastatin in the treatment of patients with Aggressive Periodontitis: A Randomized Controlled Clinical Trial. Int J PeriodonticsRestorativeDent. 2017 Mar/Apr; 37(2): e135-e141. Doi: 10.11607/prd.2936.

Rabbani GM, Ash MM, Caffesse RG. The effectiveness of subgingival scaling and root planing in calculus removal.JPeriodontol. 1981; 52(3):119-23.

Sakoda K, Yamamoto M, Negishi y, Lyao JK, Node K, Izumi Y. Simvastatin decreases IL-6 and IL-8 production in epithelial cells. J Dent Res 2006; 85:520-523.

Saxen L. Juvenile periodontitis. JClinPeriodontol 1980; 7:1-19.

Sharma A, Pradeep A.R, Clinical Efficacy of 1% Alendronate Gel in Adjunct to Mechanotherapy in the J Periodontol Treatment of Aggressive Periodontitis: A Randomized Controlled Clinical Trial, the J Periodontol. 2012 Jan; 83(1):19-26. Doi: 10.1902/jop.2011.110206. Epub 2011 May 24.

Shiloah J, Hovious LA.The role of subgingival irrigations in the treatment of periodontitis. J Periodontol.1993; 64(9):835-43.

Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta OdontolScand 964; 22:121-123.

Sindhura H, Harsha RH, Shilpa RH, Efficacy of subgingival irrigation with 10% povidone-iodine as an adjunct to scaling and root planing: A clinical and microbiological study, Send toIndian J Dent Res. 2017 Sep-Oct;28(5):514-518.

Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J ClinPeriodontol. 2018;45(Suppl 20):S149–S161

Ünsal E, Frank Walsh T, Akkaya M, The Effect of a Single Application of Subgingival Antimicrobial or Mechanical Therapy on the Clinical Parameters of Juvenile Periodontitis.J Periodontal January 1995; 66:47-51.

Yaffe A, Fine N, Alt I, Binderman I. Effect of bisphosphonate on alveolar bone resorption following mucoperiosteal flap surgery in the mandible of rats.JPeriodontol1995; 66:999-1003.

Yilmaz S, Kuru B, Noyan U, Kadir T, Acar O, Buget E, A clinical and microbiological evaluation of systemic and local metronidazole delivery in early onset periodontitis patients, Journal of Marmara University Dental Faculty, Vol 2 n 2-3, September 1996.

TABLES AND FIGURES

Table1 TheSearch strategy used in PubMed (MedLine)

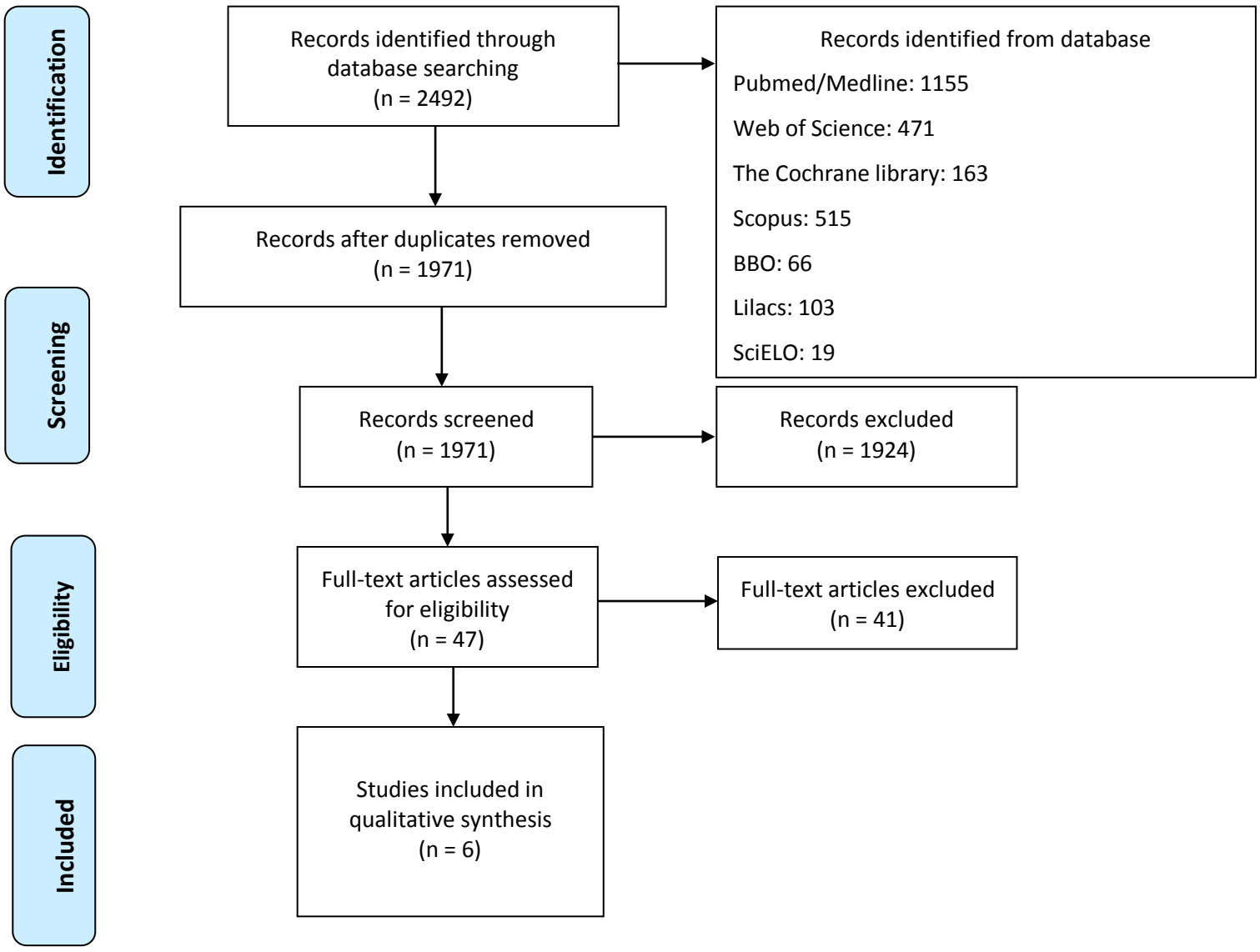
	Search
#3	#1 AND #2
#1	“Aggressive periodontitis” [MeSH] OR “Periodontitis, Aggressive” OR “Juvenile Periodontitis” OR “Periodontitis, Aggressive, 1” OR “Periodontitis, Juvenile” OR “Periodontitis, Prepubertal” OR “Prepubertal Periodontitis” OR “Early-Onset Periodontitis” OR “Periodontitis, Circumpubertal” OR “Circumpubertal Periodontitis” OR “Periodontosis” OR “Periodontoses” OR “Early Onset Periodontitis”
#2	“Scaling and root planing” [MeSH] OR “Planing, Root” OR “Planings, Root” OR “Root Planings” OR “Root planning” OR “Dental scaling” [MeSH] OR “Scaling, Dental” OR ”Scaling, Supragingival” OR “Supragingival Scaling” OR “Scaling, Root” OR “Root Scaling” OR “Root Scalings” OR “Scalings, Root” OR “Scaling, Subgingival” OR “Subgingival Scaling” OR “Periodontal treatment” OR “Periodontal therapy” OR “Anti-infective agents, local” [MeSH] OR “Agents, Local Anti-Infective” OR “Anti Infective Agents, Local” OR “Antiinfective Agents, Local” OR “Agents, Local Antiinfective” OR “Antiinfective Agents, Topical” OR “Agents, Topical Antiinfective” OR “Antiseptics” OR “Local Antiinfective Agents” OR “Topical Anti-Infective Agents” OR “Topical Anti Infective Agents” OR “Topical Antiinfective Agents” OR “Anti-Infective Agents, Topical” OR “Agents, Topical Anti-Infective” OR “Anti Infective Agents, Topical” OR “Local Anti-Infective Agents” OR “Local Anti Infective Agents” OR “Microbicides, Topical” OR “Microbicides, Local” OR “Periodontal debridement” [MeSH] OR “Debridement, Periodontal” OR “Debridements, Periodontal” OR “Periodontal Debridements” OR “Nonsurgical Periodontal Debridement” OR “Debridement, Nonsurgical Periodontal” OR “Debridements, Nonsurgical Periodontal” OR “Nonsurgical Periodontal Debridements” OR “Periodontal

Debridement, Nonsurgical" OR "Periodontal Debridements, Nonsurgical" OR "Periodontal Pocket Debridement" OR "Debridement, Periodontal Pocket" OR "Debridements, Periodontal Pocket" OR "Periodontal Pocket Debridements" OR "Periodontal pockets" [MeSH] OR "Pocket, Periodontal" OR "Periodontal Pockets" OR "Pockets, Periodontal" OR "Clinical attachment level" OR "Pocket depth" OR "Dental prophylaxis" OR "Oral prophylaxis" OR "Subgingival irrigation" OR "Antibiotics" OR "Antibiotic" OR "antibiotic prophylaxis" [MeSH]OR "Prophylaxis, Antibiotic" OR "Premedication, Antibiotic" OR "Antibiotic Premedication" OR "Antibiotic Premedications" OR "Premedications, Antibiotic" OR "Amoxicillin" [MeSH] OR "Amoxycillin" OR "Amoxicillin Trihydrate" OR "Trihydrate, Amoxicillin" OR "Hydroxyampicillin" OR "Amoxicillin Sodium" OR "Sodium, Amoxicillin" OR "Amoxicillin Monosodium Salt" OR "Amoxicillin, (R*)-Isomer" OR "Amoxil" OR "Actimoxi" OR "Clamoxyl" OR "Penamox" OR "Clamoxyl G.A" OR "G.A., Clamoxyl" OR "Clamoxyl Parenteral" OR "Parenteral, Clamoxyl" OR "Polymox" OR "Trimox" OR "Wymox" OR "Amoxicillin Anhydrous" OR "Anhydrous, Amoxicillin" OR "Amoxicilline" OR "Amoxicillin Monopotassium Salt" OR "BRL-2333" OR "BRL 2333" OR "BRL2333" OR"Metronidazole" [MeSH] OR "2-Methyl-5-nitroimidazole-1-ethanol" OR "2 Methyl 5 nitroimidazole 1 ethanol" OR "Trichazol" OR "Trichopol" OR "Trivazol" OR "Vagilen" OR "Bayer 5360" OR "Clont" OR "Danizol" OR "Flagyl" OR "Gineflavir" OR "Metric" OR "Metrodzhil" OR "MetroGel" OR "Metrogyl" OR "Metronidazole Hydrochloride" OR "Hydrochloride, Metronidazole" OR "Metronidazole Monohydrochloride" OR "Monohydrochloride, Metronidazole" OR "Metronidazole Phosphate" OR "Phosphate, Metronidazole" OR "Metronidazole Phosphoester" OR "Phosphoester, Metronidazole" OR "Satric" OR "Elyzol" OR "EDG Dentalgel" OR "Azithromycin" [MeSH] OR "Azythromycin" OR "Sumamed" OR "Toraseptol" OR "Vinzam" OR "CP-62993" OR "CP 62993" OR "CP62993" OR "Zithromax" OR "Azitrocin" OR "Azadose" OR "Ultreon" OR "Zitromax" OR "Azithromycin Dihydrate" OR "Dihydrate, Azithromycin" OR "Azithromycin Monohydrate" OR "Monohydrate, Azithromycin" OR "Goxal" OR "Zentavion"OR "Doxycycline" [MeSH] OR "Alpha-6-Deoxyoxytetracycline"

OR “Alpha 6 Deoxyoxytetracycline” OR “Doxycycline Monohydrate” OR “Doxycycline Phosphate (1:1)” OR “Oracea” OR “Periostat” OR “Vibra-Tabs” OR “Vibra Tabs” OR “VibraTabs” OR “Vibramycin” OR “Vibramycin Novum” OR “Novum, Vibramycin” OR “Vibravenos” OR “Atridox” OR “Atrigel” OR “BMY-28689” OR “BMY 28689” OR “BMY28689” OR “BU-3839T” OR “BU 3839T” OR “BU3839T” OR “Doryx” OR “Doxycycline Calcium” OR “Doxycycline Calcium Salt (1:2)” OR “Doxycycline Hyclate” OR “Hyclate, Doxycycline” OR “Doxycycline Hemiethanolate” OR “Hemiethanolate, Doxycycline” OR “Doxycycline Monohydrochloride, 6 epimer” OR “Monohydrochloride, 6 epimer” OR “Doxycycline Monohydrochloride, Dihydrate” OR “Dihydrate Doxycycline Monohydrochloride” OR “Monohydrochloride, Dihydrate Doxycycline” OR “Doxycycline-Chinoin” OR “Doxycycline Chinoin” OR “Hydramycin” OR “phenoxymethyl penicillin” [MeSH]OR “Fenoxymethylpenicillin” OR “Phenoxymethylpenicillin” OR “Penicillin, Phenoxymethyl” OR “Phenoxymethyl Penicillin” OR “Beromycin” OR “Beromycin, Penicillin” OR “Penicillin Beromycin” OR “Berromycin, Penicillin” OR “Penicillin Berromycin” OR “Betapen” OR “Pen VK” OR “Penicillin VK” OR “Penicillin V Sodium” OR “Sodium, Penicillin V” OR “V Sodium, Penicillin” OR “V-Cillin K” OR “V Cillin K” OR “VCillin K” OR “Vegacillin” OR “Apocillin” OR “Penicillin V Potassium” OR “Potassium, Penicillin V” OR “Povidone-Iodine” [Mesh] OR “Povidone Iodine” OR “Povidone-Iodines” OR “PVP-I” OR “PVP-Iodine” OR “PVP Iodine” OR “PVP-Iodines” OR “Polyvinylpyrrolidone Iodine” OR “PolyvinylpyrrolidoneIodines” OR “Betadine” OR “Betadines” OR “Providine” OR “Providines” OR “Disadine” OR “Disadines” OR “Isodine” OR “Isodines” OR “Pharmadine” OR “Pharmadines” OR “Alphadine” OR “Alphadines” OR “Betaisodona” OR “Minocycline”[MeSH] OR “Minox 50” OR “Aknemin” OR “Aknin-Mino” OR “Aknin Mino” OR “Aknosan” OR “Mynocine” OR “Apo-Minocycline” OR “Apo Minocycline” OR “Arestin” OR “Blemix” OR “Cyclomin” OR “Cyclops” OR “Dentomycin” OR “Dynacin” OR “Icht-Oral” OR “Icht Oral” OR “Klinomycin” OR “Lederderm” OR “Mestacine” OR “Minakne” OR “Mino-Wolff” OR “Mino Wolff” OR “Minocin” OR “MinocinMR” OR “Minoclir” OR “Minocycline Hydrochloride” OR “Hydrochloride, Minocycline”

OR “Minocycline Monohydrochloride” OR “Monohydrochloride, Minocycline” OR “Minolis” OR “Minomycin” OR “Minoplus” OR “Minotab” OR “Akamin” OR “Akne-Puren” OR “AknePuren” OR “Periocline” OR “Dentomicin” OR “Cetylpyridinium” [MeSH] OR “Hexadecylpyridinium” OR “Cetylpyridium” OR “Biosept” OR “Ceepryn Chloride” OR “Chloride, Ceepryn” OR “Cetamium” OR “Catamium” OR “Cetylpyridinium Chloride” OR “Chloride, Cetylpyridinium” OR “Sterogenol” OR “Dobendan” OR “Merocets” OR “Pristacin” OR “Cetylpyridinium Chloride Anhydrous” OR “Anhydrous, Cetylpyridinium Chloride” OR “Chloride Anhydrous, Cetylpyridinium” OR “Pyrisept” OR “Angifonil” OR “Cetylyre” OR “Clarithromycin”[MeSH] OR “6-O-Methylerythromycin” OR “TE-031” OR “TE 031” OR “TE031” OR “A-56268” OR “A 56268” OR “A56268” OR “Biaxin” OR “Chlorhexidine” [MeSH] OR “chlorhexidine bigluconate” OR “chlorhexidine digluconato” OR “Chlorhexidine chip” OR “Chlorhexidine gel” OR “Perio chip” OR “Peridex” OR “Hexidine” OR “Hidrocloride tetracycline” OR “Tetracycline” [MeSH] OR “Tetrabid” OR “4-Epitetracycline” OR “4 Epitetracycline” OR “Topicycline” OR “Achromycin V” OR “Hostacyclin” OR “Tetracycline Hydrochloride” OR “Tetracycline Monohydrochloride” OR “Sustamycin” OR “Actisite” OR “Achromycin” OR “Alendronate” [Mesh] OR “Aminohydroxybutane Bisphosphonate” OR “Bisphosphonate, Aminohydroxybutane” OR “4-Amino-1-Hydroxybutylidene 1,1-Biphosphonate” OR “4 Amino 1 Hydroxybutylidene 1,1 Biphosphonate” OR “Alendronate Sodium” OR “Sodium, Alendronate” OR “Alendronate Monosodium Salt, Trihydrate” OR “Fosamax” OR “MK-217” OR “MK 217” OR “MK217” OR “Xanthan” [Mesh] OR “Xanthan gum” OR “Biozan R”OR "Drugs, Chinese Herbal" [Mesh] OR “Chinese Drugs, Plant” OR “Chinese Herbal Drugs” OR “Herbal Drugs, Chinese” OR “Plant Extracts, Chinese” OR “Chinese Plant Extracts” OR “Extracts, Chinese Plant” OR "Herbal Medicine" [Mesh] OR “Medicine, Herbal” OR “Herbalism” OR "Phytotherapy" [Mesh] OR "Phytotherapy" OR “Herbal Therapy” OR “Herb Therapy” OR "Plants, Medicinal" [Mesh] OR "Plant Extracts" [Mesh] OR “Herbal”

Figure 1 Flow Diagram



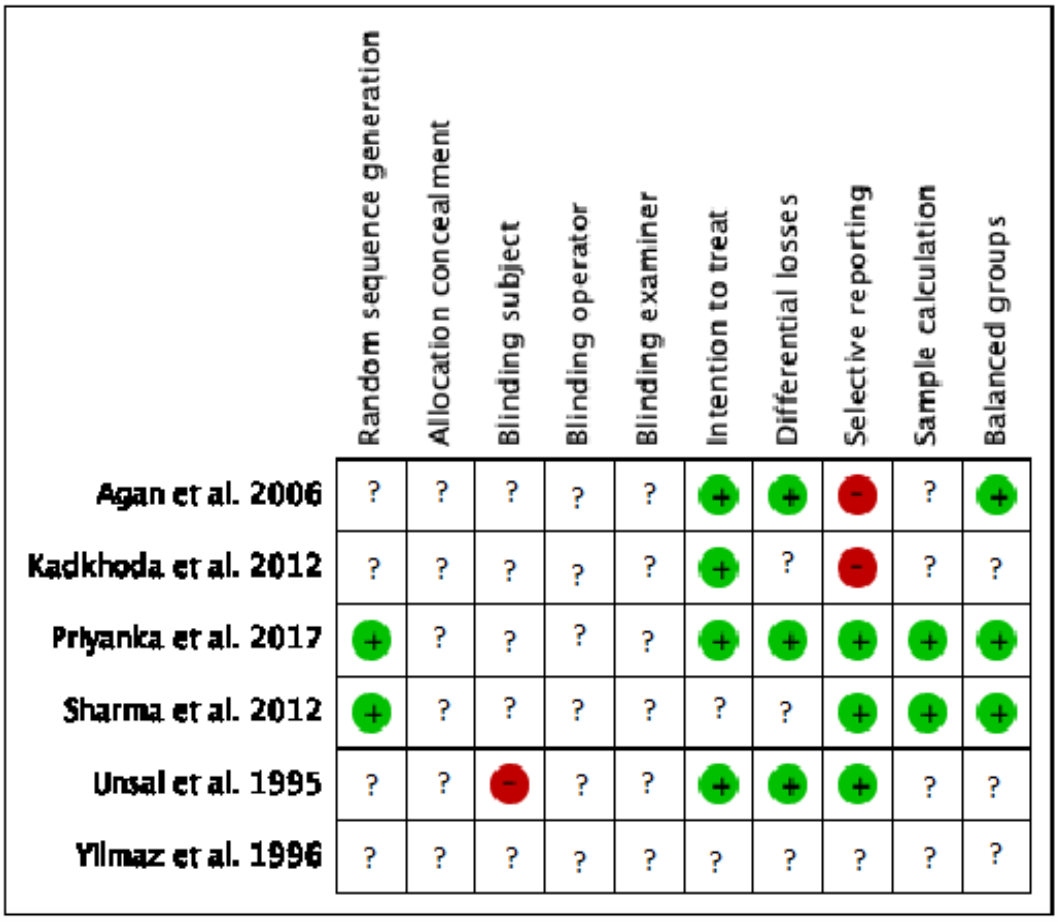


Figure 2 Summary of risk of bias (low/high/unclear)

Note:

? = unclear

= low risk

= high risk

Table 2 Demographic data, study design, duration, intervention, dosage,control, number of subjects, gender and age of included studies

Reference	Year	Country	Design of study	Duration	Intervention	Dosage	control	Number of subjects	Gender	Age
Priyanka et al.	2017	India	Parallel	180 days	1.2 mg Sinvastatin Gel	1 Irrigation after SRP	Placebo gel	24	10 ♂ and 14 ♀	30-50
Sharma et al.	2012	India	Parallel	180 days	Alendronate gel (10 mg/mL)	1 Irrigation after SRP	Placebo gel	20	12 ♂ and 8 ♀	20-35
kadkhoda et al.	2012	Iran	Split mouth	90 days	25% metronidazole gel (elyzol)	1 Irrigation after SRP + 1 week later	Only SRP	20	7 ♂ and 13 ♀	20-42
Agan et al.	2006	Turquia	split mouth	180 days	10% Doxycycline Hyclate gel	1 Irrigation after SRP	Only SRP	8	4 ♂ and 4 ♀	19-31
yilmaz et al.	1996	Turquia	Parallel	42 days	25% metronidazole gel (elyzol)	1 Irrigation after SRP	Only SRP	6	NR	19-25
Unsal et al.	1995	Turquia	Parallel	90 days	40% tetracycline hydrochloride and 1% Chlorhexidine digluconate gel	1 Irrigation after SRP	Only SRP	26	NR	16-25

SRP scaling and root planning; ♂ male; ♀ female; NR not reported.

Table3 Mean of Dental plaque, Gingival Inflammation, Probing Bleedingof the included studies

Study		Dental plaque (DP) Mean (SD)			Gingival Inflamation (GI) Mean (SD)			Probing Bleeding (PB) Mean (SD)			Index
		Intervention 1	Intervention 2	Control	Intervention 1	Intervention 2	Control	Intervention 1	Intervention 2	Control	
		SMV gel (1.2 mg/0.1 mL)		Placebo gel	SMV gel (1.2 mg/0.1 mL)		Placebo gel	SMV gel (1.2 mg/0.1 mL)		Placebo gel	
	Baseline	1.98 (0.24)		1.87 (0.22)	2.79 (0.28)		2.79 (0.28)				PI (S & L)
	1 month										(mSBI) (Mombelli 1984)
Priyanka et al. (2017)	3 month	0.92 (0.32)		0.81 (0.16)	1.22 (0.94)		2.39 (0.27)				
	6 month	0.75 (0.21)		0.66 (0.13)	1.25 (0.19)		2.56 (0.15)				
	ΔSD	_1.23 (0.31)		_1.21 (0.25)	_1.54 (0.33)		_0.23 (0.31)				
	%	62.20%		64.71%	55.19%		8.24%				
		ALN gel (10 mg/mL)		Placebo gel	ALN gel (10 mg/mL)		Placebo gel	ALN gel (10 mg/mL)		Placebo gel	
	Baseline	0.89 (0.51)		0.93 (0.37)	2.51 (0.54)		2.43 (0.78)				PI (S & L)
	1 month										(mSBI) (Mombelli 1984)
Sharma et al. (2012)	3 month										
	6 month	0.30 (0.27)		0.51 (0.35)	0.60 (0.53)		0.94 (0.46)				
	ΔSD	_0.59 (0.57)		_0.42 (0.50)	_1.91 (0.75)		_1.49 (0.90)				
	%	65.11%		45.16%	76.09%		61.31%				
		metronidazole gel 25% (elyzol)		Only SRP	metronidazole gel 25% (elyzol)		Only SRP	metronidazole gel 25% (elyzol)		Only SRP	
	Baseline							2.74 (0.57)		2.80 (0.65)	
	1 month										
kadkhoda et al. (2012)	3 month							0.15 (0.51)		0.52 (0.52)	
	6 month										
	ΔSD							_2.54 (0.76)		_2.28 (0.83)	
	%							94.52%		81.42%	
		10% Doxycycline		Only SRP				10% Doxycycline		Only SRP	
	Baseline	3.63 (0.74)		3.51 (0.76)				3.63 (0.52)		3.54 (0.53)	PI (S & L)
	1 month										
Agan et al. (2006)	3 month										
	6 month										
	ΔSD										
	%										
		Metronidazole gel 25% (elyzol)		Only SRP	Metronidazole gel 25% (elyzol)		Only SRP				
	Baseline	1.70 (0.60)		1.60 (0.90)	1.9 (0.50)		1.9 (0.7)				PI (S & L)
	42 days	0.90 (0.70)		0.70 (0.60)	0.9 (0.30)		1 (0.5)				GI (LOE 1963 e sillnes)
yilmaz et al. (1996)	3 month										
	6 month										
	ΔSD	_0.80 (0.92)		_0.90 (1.08)	_1.00 (0.58)		_0.90 (0.86)				
	%	47.05%		56.25%	52.63%		47.36%				
		40% Tetracycline	1% Chlorhexidine	Only SRP	40% Tetracycline	1% Chlorhexidine	Only SRP	40% Tetracycline	1% Chlorhexidine	Only SRP	
	Baseline	1.22 (0.37)	1.06 (0.35)	1.10 (0.23)	2.79 (0.28)	0.84 (0.28)	2.86 (0.46)	49.28 (22.92)	37.84 (10.82)	47.12 (8.21)	PI (S & L)
	1 month										GI (LOE 1963 e sillnes)
Unsal et al. (1995)	3 month	0.33 (0.18)	0.54 (0.37)	0.60 (0.33)	0.32 (0.21)	0.42 (0.19)	0.55 (0.17)	7.21 (6.69)	5.86 (3.63)	10.12 (2.52)	BI (klaus 1989)
	6 month										
	ΔSD	_0.89 (0.41)	_0.52 (0.50)	_0,50 (0.40)	_2.47 (0.35)	_0.42 (0.33)	_2.31 (0.49)	_42.07 (23.87)	_31.98 (11.41)	_37.00 (8.58)	
	%	72.95%	49.05%	45.45%	88.53%	50.00%	80.76%	85.36%	84.51%	78.52%	

Δ, delta of mean (final – initial mean) and delta of standard deviation (SD); %, percentage of reduction GI (L& S): Gingival Index (LÖE& SILNESS 1963); Pl (S & L): Plaque index (SILNESS & LÖE, 1964); m SBI modified sulcus bleeding index (Mombelli et al.1987); BI Bleeding Index (Klaus et al. 1989); SRP Scaling and root planing;

Table 4 Mean of Probing Depth and CAL of the included studies

Study		PD (mm) Mean (SD)			CAL (mm) Mean (SD)			Author´s Conclusions
		Intervention 1	Intervention 2	Control	Intervention 1	Intervention 2	Control	
Priyanka et al. (2017)		**SMV gel (1.2 mg/0.1 mL)**		**Placebo gel**	**SMV gel (1.2 mg/0.1 mL)**		**Placebo gel**	Local delivery of SMV gel into the periodontal pocket stimulated a signifcante increase in PD reduction and CAL gain and improved bone fill compared to the control group.
	Baseline	6.93 (1.37)		6.70 (1.21)	7.85 (1.45)		7.22 (1.42)	
	1 month							
	3 month	4.11 (0.83)		5.12 (1.33)	4.17 (1.23)		6.13 (0.87)	
	6 month	3.15 (0.75)		5.56 (1.25)	3.99 (1.04)		5.86 (0.62)	
	Change	3.78 (0.62)		1.14 (0.04)	3.86 (1.78)		1.36 (1.54)	
Sharma et al. (2012)		**ALN gel (10 mg/mL)**		**Placebo gel**	**ALN gel (10 mg/mL)**		**Placebo gel**	The results of the present study show local delivery of 1% ALN stimulates a significant increase in PD re- duction, CAL gain, and improved bone fill compared to placebo gel as an adjunct to scaling and root planing in patients with AgP.
	Baseline	7.85 (2.20)		7.69 (2.22)	6.12 (1.77)		5.96 (1.88)	
	2 month	6.04 (1.99)		6.96 (2.10)	4.46 (2.43)		5.19 (2.29)	
	3 month							
	6 month	3.96 (1.28)		6.04 (1.68)	2.85 (1.82)		4.54 (2.12)	
	Change	3.88 (1.39)		1.65 (1.35)	3.27 (1.11)		1.42 (1.70)	
kadkhoda et al. (2012)		**metronidazole gel 25% (elyzol)**		**Only SRP**	**metronidazole gel 25% (elyzol)**		**Only SRP**	The case group patients had significantly better results in BOP, PPD. According to the measurements of CAL, the statistical difference was non significant (p>0.05)
	Baseline	6.09 (1.13)		6.30 (1.55)	5.17 (1.43)		5.61 (2.02)	
	1 month							
	3 month	3.02 (0.91)		3.76 (1.21)	7.72 (1.89)		7.83 (2.51)	
	6 month							
	Change	3.07 (1.45)		2.54 (1.96)	_2.55 (2.37)		_2.22 (3.22)	
Agan et al. (2006)		**10% Doxycycline**		**Only SRP**	**10% Doxycycline**		**Only SRP**	There was no statistically significant difference between the mean pocket depth reducton. The improvements of CAL did not have statiscally significant difference either between the groups at each time points, or when compared with the baseline.
	Baseline	6.99 (0.68)		6.94 (0.76)	8.05 (0.64)		7.94 (0.82)	
	1 month	3.51		3.84	6.32		6.34	
	3 month	3.63		4	6.42		6.44	
	6 month	3.88		4.19	6.5		6.54	
	Change	3.11		2.75	1.55		1.40	
Yilmaz et al. (1996)		**metronidazole gel 25% (elyzol)**		**Only SRP**	**metronidazole gel 25% (elyzol)**		**Only SRP**	Mean probing pocket depth changes were significant from baseline in all groups. SRP plus metronidazole delivery revelead higher values in attachement gain.
	Baseline	6.00 (0.50)		5.90 (0.60)	9.20 (1.50)		9.10 (2.00)	
	42 days	3.90 (0.50);		4.5 (1.0)	8.30 (1.40)		8.40 (2.10)	
	3 month							
	6 month							
	Change	2.10 (0.60)		1.40 (0.60)	0.90 (0.60)		0.80 (0.30)	
Unsal et al. (1995)		**40% tetracycline**	**1% Chlorhexidine**	**Only SRP**	**40% tetracycline**	**1% Chlorhexidine**	**Only SRP**	All treatment modalities resulted in a pronounced improvement in PI, GI, and GI-S by 12 weeks (P <0.001). The mean probing depths also decreased, but there were no significant-differences found between the three groups. It was concluded that a single application of topical subgingival tetracycline did not result in any short-term improve- ment over that achieved by standard non-surgical therapy in the clinical parameters of these localized juvenile Periodontitis patients.
	Baseline	4.35 (0.88)	4.21 (0.97)	4.88 (0.76)	3.44 (0.95)	3.05 (1.58)	3.35 (0.74)	
	1 month							
	3 month	3.09 (0.58)	3.10 (0.77)	3.06 (0.46)	2.13 (0.69)	2.10 (1.08)	2.10 (1.08)	
	6 month							
	Change	1.25 (0.80)	1.10 (0.95)	1.81 (0.75)	1.31 (0.68)	0.95 (1.00)	1.16 (0.55)	

Change (initial – final mean); PD Probing depth; CAL Clinical attachment level; SMV Simvastatin; ALN Alendronate; AgP Aggressive periodontitis; SRP Scaling and root planning

7Anexo

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

Use of antimicrobial agents as a adjuvant to conventional periodontal treatment in cases of aggressive periodontitis

Edvin Gomes, Thiago Martins, Adriana Silva

Citation
Edvin Gomes, Thiago Martins, Adriana Silva. Use of antimicrobial agents as a adjuvant to conventional periodontal treatment in cases of aggressive periodontitis. PROSPERO 2018 CRD42018092434 Available from:
http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018092434

Review question
Does the use of antimicrobial agents as a adjuvant to conventional periodontal treatment lead to clinical evidence of periodontal tissue repair in cases of aggressive periodontitis?

Searches
The search strategy will include only terms relating to or describing the intervention. The terms will be combined with the Cochrane MEDLINE filter for controlled trials of interventions. The search strategy for MEDLINE is available in the published protocol. The search terms will be adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these are available.

Types of study to be included
Clinical trials and Retrospective Studies

Condition or domain being studied
Periodonta deseases. Aggressive periodontitis

Participants/population
Inclusion: Adults with aggressive periodontitis

Exclusion Adolescents (under 18 years of age) and elderly people (over 70)

Intervention(s), exposure(s)
Adults with aggressive periodontitis who underwent conventional periodontal treatment as the use of antimicrobial ague as a coadjuvant

Comparator(s)/control
Periodontally healthy adults

Context

Main outcome(s)
use of antimicrobial agents as a adjuvant to conventional periodontal treatment leads to improvements in the clinical picture of depth of probing and level of clinical insertion of patients with aggressive periodontitis

Timing and effect measures

depth of probing and level of clinical insertion

Additional outcome(s)
None

Timing and effect measures

None

Data extraction (selection and coding)