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Comparative Effectiveness Research of Adjunctive Methods in Controlling Peri-Implant Mucositis Intervention A Systematic Review Analysis

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Comparative Effectiveness Research of Adjunctive Methods in Controlling Peri-Implant Mucositis Intervention

A Systematic Review Analysis

A thesis submitted in partial satisfaction

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in Oral Biology

by

Shadi Javadi

2017

ABSTRACT OF THE THESIS

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Controlling Peri-Implant Mucositis Intervention
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by

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Master of Science in Oral Biology

University of California, Los Angeles, 2017

Professor Francesco Chiappelli, Chair

Introduction and Objective: Peri-implant mucositis is a very common condition affecting the gingival tissue around dental implants. It is an inflammation of the tissues, characterized by bleeding on probing around the implant. This condition is the initial step of a more severe condition called peri-implantitis, which is very difficult to treat. With increased number of implant placements in patients, the length of time each dental implant is supposed to serve, and the price of replacing the implant after failure, the importance of maintaining a healthy tissue around implants has become a fundamental issue. Mechanical debridement is the proposed treatment of peri-implant mucositis, which may be accompanied by adjunctive methods to increase the efficacy

of treatment. These options include but are not limited to photodynamic therapy, chlorhexidine, antibiotics, etc.

Due to the importance and prevalence of peri-implant mucositis, the establishment of a treatment protocol is called for. If the addition of adjunctive treatments reduces the inflammation, they can be added to the mechanical debridement approach. Since there are multiple adjunctive methods, there is a need to conduct a comparative effectiveness research to provide scientific information regarding the best option. The aim of this study is to find out whether addition of adjunctive methods to mechanical debridement improves the results of controlling peri-implant mucositis. This improvement can be measured by bleeding on probing scores before and after the intervention.

Methods: Search for systematic reviews, observational studies, and randomized clinical trials studies was done using the National Library of Medicine-PubMed, Cochrane library, the American Dental Association (ADA) web Library, and hand search. The relevance of the identified systematic reviews and clinical trials studies to the study and PICOTS questions was assessed using the inclusion and exclusion criteria. The quality of evidence was achieved using the CONSORT-2010 checklist instrument.

Results: Three out of five randomized clinical trials were considered as high quality studies. We were unable to perform a Meta-analysis due to the heterogeneity in the methods and results of the retained articles.

Conclusion: Based on the results of the three retained randomized clinical trials, chlorhexidine might or might not reduce the bleeding on probing scores around dental implants and antibiotics showed no short term differences.

The thesis of Shadi Javadi is approved.

Renate Lux

Carl Maida

Francesco Chiappelli, Committee Chair

University of California, Los Angeles

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Chapter 1

Introduction

1. Peri-implant mucositis

1.1. Definition of peri-implant mucositis:

Today dental implants are utilized widely in dental treatments. Despite their overall success, failure is also a possible outcome. Therefore, it is essential to treat implant diseases to prevent implant loss. Peri-implant disease is classified into two forms, peri-implant mucositis and peri-implantitis. Peri-implant mucositis is inflammation of peri-implant soft tissues and peri-implantitis includes additional loss of bone (Laney et al., 2007). Peri-implant mucositis is defined as a reversible inflammation of the soft tissues without pathologic bone loss. Clinical signs include bleeding and/or suppuration on probing and increased probing depths (4–5 mm) (Albrektsson et al., 1994). Clinical features of this condition include swelling, redness, and bleeding upon light probing of soft tissues (Berglundh et al., 2011, Costa et al., 2011, Lindhe et al., 2008).

1.2. Prevalence of peri-implant mucositis:

Peri-implant mucositis might involve up to 80% of patients with dental implants

(Koldsland et al., 2010, Rinke et al., 2011, Zitzmann et al., 2008). Other studies reported the prevalence of this condition up to 64% (Atieh et al., 2012, Lindhe et al., 2008).

Prevalence of peri-implant mucositis and peri-implantitis has also been reported as 43% and 22%. These data ranged from 19% to 65% and from 1% to 47%, due to the differences in the disease definitions (Derks & Tomasi, 2015).

1.3. Mechanism of peri-implant mucositis:

Peri-implant mucositis is an inflammatory process caused by oral microflora and immune system reaction around implants characterized by bleeding on probing, with pocket depths of 4mm or more, no bone loss other than normal, and possible suppuration. It is considered to be reversible after mechanical cleaning (Rosen et al., 2013).

Peri-implant mucositis is caused by the host response to bacterial invasion, which is similar to gingivitis around teeth (Heitz-Mayfield & Lang, 2010). Inflammatory infiltrations in both conditions show common histological characteristics (Berglundh et al., 1992, Ericsson et al., 1992, Trejo et al., 2006). It was also reported that after 3 months, the inflammatory infiltrate of the peri-implant mucosa is almost 3 times more than the one found around teeth (Berglundh et al., 1992, Ericsson et al., 1992, Heitz-Mayfield & Lang, 2010).

1.4. Etiology and predisposing factors:

Due to the reduced vascularization and parallel orientation of the collagen fibers, peri-implant tissues are more susceptible to inflammation compared to tissues around teeth and increased formation of inflammatory infiltrate, nitric oxide 1/3, VEGF, lymphocytes, leukocytes, and Ki-67 (Degidi et al., 2012), in addition to an increased level of matrix-metalloproteinases (MMP) is noticed (Sorsa et al., 2010, Sorsa et al., 2011, Xu et al., 2008).

Peri-implant mucositis is caused by dental plaque accumulation (Pontoriero et al., 2014, Salvi et al., 2012, Zitzmann et al., 2001). The primary etiology of peri-implant disease is oral bacteria (Persson et al., 2011). Peri-implant soft tissues respond with an inflammatory cell infiltrate to microorganisms in the biofilm (Berglundh et al., 2008). Peri-implant mucositis is the result of host's response to bacteria (Heitz-Mayfield & Lang, 2010). If peri-implant mucositis is left untreated, it can progress to peri-implantitis (Pontoriero et al., 1994). A number of pathogenic bacteria has been identified in peri-implant diseases including *Prevotella intermedia*, *Prevotella nigrescens*, *Streptococcus constellatus*, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (Rams et al., 2013, Zitzmann et al., 2006).

It is important to identify susceptible patients with greater risk for peri-implantitis and put an extra effort to maintain the health of peri-implant tissues. A number of studies indicated that patients with a previous history of periodontitis or tooth loss due to periodontitis are at

a greater risk for developing peri-implantitis (Brocard et al., 2000, Evian et al., 2004, Hanggi et al., 2005, Hardt et al., 2002, Karoussis et al., 2003, 2004, Mengel et al., 2005, Roos-Jansaker et al., Rosenberg et al., 2006, Schou et al., 2006, Van der Weijden et al., 2005).

There are several risk factors for peri-implant diseases including smoking (Anner et al., 2010), diabetes mellitus (Anner et al., 2010), remaining cement, previous periodontal disease, poor oral hygiene, genetic factors, and excessive occlusal forces (Rosen et al., 2013).

Diabetes is one of the risk factors of periodontal diseases (Monje et al., 2017). The chronic inflammatory responses to bacteria and diabetes adversely affect each other (Bartold & Van Dyke, 2013, Borgnakke, 2016, Loos, 2005) and the elevated blood glucose levels contribute to impaired tissue repair (Lalla & Papapanou, 2011). Diabetes facilitates attachment loss and persistent bone resorption (Chang et al., 2012, Chang et al., 2013). Hyperglycemia affects wound healing. Hyperglycemia is also associated with hyper-inflammatory responses (Hasturk & Kantarci, 2015).

Remaining cement is another important risk factor which might contribute to the progression of peri-implantitis due to its roughness (which can cause inflammation) or due to providing a suitable environment for bacterial attachment. Some of the cements are radiolucent and are not visible on radiographs. If possible, using screw-retained restorations and avoiding cement extrusion might be helpful in preventing peri-implant diseases (Robertson et al., 2015).

Occlusal overload is another risk factor which is caused by the prosthetic design. It is very difficult to define and quantify the trauma by this force clinically over the lifetime of the implant (Robertson et al., 2015).

Additionally, genetic factors play a role in peri-implant diseases. The host response to bacteria is influenced by host genes. Pathogenic bacteria stimulate pro-inflammatory cytokines and coordinate the local inflammatory response (De Mendonca et al., 2009). There is potential for genetic alterations of any of the above factors to influence patient susceptibility to peri-implantitis (Robertson et al., 2015).

Smoking is a very important risk factor in peri-implant disease since it may alter the immune-inflammatory system (Rom et al., 2013). Smoking might affect the normal inflammatory healing response by reducing the inflammatory chemotactic response, migratory function, and oxidative bactericidal mechanisms (Sørensen et al., 2012). A number of studies have indicated negative effects of smoking on peri-implantitis (Haas et al., 1996, Heitz-Mayfield et al., 2008, Heitz-Mayfield et al., 2009, Mombelli et al., 2012, Strietzel et al., 2007).

History of periodontal disease in patients is another contributing factor to occurrence of peri-implant diseases. Previous periodontal disease might be the reason for tooth extraction in the first place which might increase the incidence of peri-implantitis (Rosen et al., 2013). Additionally, periodontal disease affects the quality of the patient's biofilm and

change it from low total bacterial load and primarily gram-positive cocci towards an increased total bacterial load and increased *Aggregatibacter actinomycetemcomitans*, *Fusobacterium species*, *Prevotella intermedia*, *Porphyromonas gingivalis*, mobile organisms, and spirochetes, which cause peri-implant diseases (Ata-Ali et al., 2011).

Poor oral hygiene may also be the result of different reasons such as improper prosthetic design which might makes cleaning harder for patients (Robertson et al., 2015).

1.5. Diagnosis and assessment methods:

The following factors may be used for peri-implant mucositis assessment: presence of plaque and calculus, probing depth measurements, presence or absence of bleeding on probing/suppuration, and radiographic assessment (Lang et al., 2004).

Signs of peri-implant mucositis include color changes and bleeding on probing. Evaluation of oral hygiene and a reevaluation after mechanical debridement should be done after thirty days. If clinical signs of inflammation still exist, a check for excess cement should be done (Wilson et al., 2014). Radiographs are used to assess bone levels and periodontal probe is used to assess pocket depths and bleeding on probing.

Additionally, bleeding on probing was stated to be useful in determining health and disease of peri-implant tissues and to evaluate treatments (Jepsen et al., 2015).

1.6. Peri-implant mucositis treatment:

The main goal of treatment of peri-implant disease is to control the infection and to prevent disease progression. Treatment of peri-implant mucositis requires removal of plaque and calculus. In addition, oral hygiene instructions should be provided (Heitz-Mayfield, 2008).

Routine maintenance of implants is important. This includes taking radiographs, probing depth, checking the occlusion, and oral hygiene (Sgolastra et al., 2013). Peri-implant mucositis is reversible (Salvi et al., 2012), but it may lead to peri-implantitis which is hard to control and lead to failure. Therefore, the resolution of inflammation by an effective treatment is a very pressing matter.

1.6.1. Mechanical debridement:

This method is used to remove plaque/calculus from around implants. Other methods are added to enhance the effect of mechanical cleaning. After mechanical debridement, bleeding on probing may still be found around implants (Heitz-Mayfield et al., 2011).

1.6.2. Adjunctive methods:

a. Antiseptic therapy:

Chlorhexidine, EDTA, citric acid, hydrogen peroxide, and many others are included in this

group (Froum et al., 2012, Khoury et al., 2001, Roccuzzo et al., 2011, Schmidt et al., 2014, Suarez et al., 2013, Waal et al., 2013).

b. Antibiotic therapy:

The addition of systemic/local antibiotics including amoxicillin, metronidazole, clindamycin, augmentin, tetracycline, bactrim, and ciprofloxacin, or a combination of these to the mechanical debridement are in this group. This option primarily focuses on anaerobic gram-negative bacteria (Heitz-Mayfield et al., 2014). Antibiotics with broad-spectrum anti-infectious and anti-inflammatory properties may help in controlling the peri-implant diseases (Hallström et al., 2012).

c. Photodynamic therapy:

Photodynamic therapy (PDT) has been used to treat periodontal and peri-implant disease (Sgolastra et al., 2013, Talebi et al., 2016). Its bactericidal properties is due to free reactive oxygen specimens produced by the light activation of a dye (Konopka & Goslinski, 2007, Takasaki et al., 2009).

2. Evidence-based dentistry:

Evidence-based dentistry is a systematic approach to oral health care that integrates patient needs, clinician's expertise, and relevant scientific evidence to come up with recommendations for stake holders. This approach considers the efficacy, safety, and

cost of alternatives (Chiappelli, 2014).

Evidence based dentistry relies on a systematic process of research synthesis that aims to develop a comparative efficacy and effectiveness research, comparing benefits and harms of different interventions to treat, diagnose, or monitor a health condition and to recognize the best available evidence to support health care modalities (Chiappelli & Danaei, 2012).

This systematic process starts with a research question and a hypothesis, which defined the population of interest, the intervention, the comparator, and the clinical outcome, within a given timeline and clinical setting. By using the elements of the research question, the keywords are extracted and inclusion/exclusion criteria are created. After forming the bibliome, irrelevant evidence that does not fit within the PICOTS question and the inclusion/exclusion criteria are excluded. Afterwards, assessment of the quality of the retrieved evidence is performed with validated reliable grading instruments intended to evaluate the level of evidence (AHRQ, Methods Guide for Effectiveness and Comparative Effectiveness Reviews, 2014).

The next step is data analysis and acceptable sampling analysis to retain the highest quality level of evidence. Finally, the consensus of the best available evidence is reported in scientific form as a scientific review (Chiappelli, 2014).

3. Purpose of the study:

The aim of the study is to conduct a comparative effectiveness research to find the best available evidence in support of mechanical cleaning plus adjunctive methods being more effective in reducing inflammation than mechanical cleaning alone. This purpose drives the following PICOTS questions:

Population: Adult patients, diagnosed with peri-implant mucositis (bleeding on probing on 1 or more aspects of implant), no history of immunocompromising diseases or uncontrolled diabetes.

Intervention: Mechanical cleaning to reduce inflammation (bleeding on probing)

Comparator: Mechanical cleaning plus adjunctive methods

Outcome: Reduced inflammation (bleeding on probing) (assessed by probing with a probe on 4-6 sides around implant and reporting the changes in percentages)

Timeline: Evaluation after 4-6 weeks after intervention

Setting: Any clinical practice (university/private practice)

Chapter 2

Methodology

1. Hypothesis:

a. **Research Hypothesis:** Mechanical cleaning with adjunctive methods are more effective in controlling peri-implant mucositis compared to mechanical cleaning alone.

b. **Correlative Hypothesis:** Antibiotics and lasers are more effective amongst adjunctive methods in controlling peri-implant mucositis.

2. Analytical framework:

The analytic framework represents relevant clinical concepts and refines the relationship between outcome measures and health outcomes. It helps to understand clinical decisions (AHRQ, Methods Guide for Effectiveness and Comparative Effectiveness Reviews, 2014).

The elements of the analytical framework are presented in figure 1 in the end. Analytical framework was developed using with following key questions:

1. Does addition of adjunctive methods improve the effect of mechanical cleaning?

2. Does any of adjunctive methods show better results in controlling peri-implant mucositis

compared to the rest?

3. How do diabetes, smoking, and oral hygiene effect the final outcome?

4. What are the possible adverse effects of adjunctive methods?

3. Search Strategy:

The search for systematic reviews, observational studies, and randomized clinical trials studies was done in June 2017 via electronic bibliographic databases using the following keywords:

a. Peri-implant mucositis,

b. Nonsurgical intervention,

c. Mechanical debridement,

d. Scaling,

e. Ultrasonic,

f. Air power Abrasive,

g. Pumice,

h. Rubber cup,

i. Polishing.

The Medical Subject Headings (MeSH) and Text Words used to perform the search strategy were as following:

((peri-implant [text word] AND mucositi*[text word]) OR Peri-implantitis [MeSH] OR Mucositis [MeSH]) AND ("Dental Prophylaxis"[mesh] OR Nonsurgical intervention [text word] OR mechanical debridement [text word] OR Scal*[text word] OR Ultrasonic [text word] OR Air power Abrasive [text word] OR Pumice [text word] OR Rubber cup [text word] OR Polishing [text word]).

3.1. Search for systematic reviews, randomized clinical trials, and observational studies:

The following search engines were explored:

A. The National Library of Medicine-PubMed,

B. Cochrane library,

C. American Dental Association (ADA) web Library.

4. Determination of the Relevance:

The relevance of the identified systematic reviews and clinical trials to the study and PICOTS question was assessed using the following criteria:

4.1. Inclusion Criteria:

a. >18 year old patients with peri-implant mucositis
b. Systematic reviews, observational studies, and clinical trials
c. English language studies
d. Evaluation after 4-6 weeks of intervention
e. Bleeding on probing percentage assessment before and after treatment

4.2. Exclusion Criteria:

f. Animal studies
g. Non-English language papers
h. Immunocompromising systemic diseases or uncontrolled diabetes
i. Peri-implantitis (diagnosed by bone loss)
j. Implant failure/extraction

4.3. Adherence to the proposed PICOTS question:

The PICOTS questions were applied to the methodology and results of each study to filter papers after applying the inclusion and exclusion criteria and to determine the faithfulness of each identified paper in the bibliome.

The following lines describe the characteristics of the PICOTS questions:

- Population: adult patients diagnosed with peri-implant mucositis (bleeding on probing on one or more aspects of implant), no history of immunocompromising diseases or uncontrolled diabetes
- Intervention: mechanical cleaning to reduce inflammation (bleeding on probing)
- Comparator: mechanical cleaning plus adjunctive methods
- Outcome: reduced inflammation (bleeding on probing) assessed by probing with a probe on 4-6 sides around implant and reporting the changes in percentages.
- Timing: evaluation after 4-6 weeks
- Setting: any clinical practice (university or private practice)

5. Measurements:

The quality of evidence and clinical relevance analysis was achieved using a validated and reliable instrument, the CONSORT-10 checklist.

5.1. Quality of Clinical Trials:

The CONSORT 2010 checklist instrument was utilized to assess and quantify the quality of the retained clinical trials (Chulz et al., 2010). It includes 37 questions. Each question was answered with “yes” or “no”. Each “yes” answer received a score of 2 and each “no”

answer received a score of 1. The total scores were counted for each study.

5.2. CONSORT 2010 checklist items:

-Title and abstract:

1a Identification as a randomized trial in the title

1b Structured summary of trial design, methods, results, and conclusions

-Introduction:

Background and objectives:

2a scientific background and explanation of rationale

2b specific objectives or hypotheses

-Methods:

Trial design:

3a description of trial design (such as parallel, factorial) including allocation ratio

3b important changes to methods after trial commencement (such as eligibility criteria), with reasons.

Participants:

4a eligibility criteria for participants

4b settings and locations where the data were collected

Interventions:

5 the interventions for each group with sufficient details to allow replication, including how and when they were actually administered

Outcomes:

6a completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed

6b any changes to trial outcomes after the trial commenced, with reasons

Sample size:

7a how sample size was determined

7b when applicable, explanation of any interim analyses and stopping guidelines

Randomization: Sequence generation

8a method used to generate the random allocation sequence

8b type of randomization; details of any restriction (such as blocking and block size)

Allocation concealment mechanism:

9 mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned

Implementation:

10 who generated the random allocation sequence, who enrolled participants, and who

assigned participants to interventions?

Blinding:

11a if done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how

11b if relevant, description of the similarity of interventions

Statistical methods:

12a statistical methods used to compare groups for primary and secondary outcomes

12b methods for additional analyses, such as subgroup analyses and adjusted analyses

- Results:

Participant flow (a diagram is strongly recommended):

13a for each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome

13b for each group, losses and exclusions after randomization, together with reasons

Recruitment:

14a dates defining the periods of recruitment and follow-up

14b why the trial ended or was stopped

Baseline data:

15 a table showing baseline demographic and clinical characteristics for each group

Numbers analyzed:

16 for each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Outcomes and estimation:

17a for each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)

17b for binary outcomes, presentation of both absolute and relative effect sizes is recommended

Ancillary analyses:

18 results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Harms:

19 all important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

- **Discussion:**

Limitations:

20 trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

Generalizability:

21 generalizability (external validity, applicability) of the trial findings

Interpretation:

22 interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

-Other information:

Registration:

23 registration number and name of trial registry

Protocol:

24 where the full trial protocol can be accessed, if available

Funding:

25 sources of funding and other support (such as supply of drugs), role of funders.

5.3. Acceptable Sampling Analysis

The bibliome showed a considerable heterogeneity in terms of quality of the evidence. A cut off of the low quality studies was required to obtain the most homogenously scored articles that represents a higher score and the higher quality studies. The top 20%

highest scoring papers in the Bibliome were accepted. Only three papers were accepted, which then were used to extract data. The qualitative consensus of the best available evidence was established.

Chapter 3

Results

1. Search Results and Determination of the Relevance:

1.1. Search for Systematic Reviews:

The initial retained systematic reviews were not relevant to this project's PICOTS questions and therefore were not included. These studies either included animal studies in their conclusions or they included studies with re-evaluation period time of more than 4-6 weeks. Hence, they did not meet the PICOTS questions' criteria.

1.2. Search for Randomized Clinical Trials and Observational Studies:

Figure 2 shows the summary of randomized clinical trial studies selection process. The initial search for randomized clinical trials and observational studies was done using PubMed, Cochrane central, and ADA website search engine in addition to hand search. After duplicates removal, applying the inclusion/exclusion criteria, and obtaining studies which were relevant to the PICOTS questions, five randomized clinical studies were retained:

- A clinical study of the effect of chlorhexidine gel in addition of mechanical cleaning in controlling peri-implant mucositis (Hallström et al., 2015).
- A clinical study of the effect of systemic antibiotics in addition of mechanical cleaning in controlling peri-implant mucositis (Hallström et al., 2012).
- A clinical study of the effect of chlorhexidine gel in addition of mechanical cleaning in controlling peri-implant mucositis (Heitz-Mayfield et al., 2011).
- A clinical study of the effect of chlorhexidine gel in addition of mechanical cleaning in controlling peri-implant mucositis (Thöne-Muhling et al., 2010).
- A clinical study of the effect of chlorhexidine gel in addition of mechanical cleaning in controlling peri-implant mucositis (Porras et al., 2002).

2. Measurements and Quality Assessment:

2.1. Quality of Clinical Trials:

Table 1 shows the score of each clinical trial. The CONSORT 2010 checklist instrument was utilized to evaluate the quality of the five retained clinical trials. A cut off of the low quality studies was required to obtain the most homogenous scored articles that represent a higher score and the higher quality studies. The top 20% highest scoring papers in the bibliome were accepted.

3. Data Analysis:

3.1. Acceptable Sampling (Quality of the Clinical trials):

Figure 1 shows the CONSORT-10 checklist scores for clinical trials. The top 20% highest scoring papers in the bibliome were accepted. Out of the five retained articles, a cut off of the low quality studies yielded the top three scoring articles as high quality studies due to the big gap in their scores compared to the other two articles:

- A clinical study of the effect of chlorhexidine gel in addition of mechanical cleaning in controlling peri-implant mucositis (Hallström et al., 2015).
- A clinical study of the effect of systemic antibiotics in addition of mechanical cleaning in controlling peri-implant mucositis (Hallström et al., 2012).
- A clinical study of the effect of chlorhexidine gel in addition of mechanical cleaning in controlling peri-implant mucositis (Heitz-Mayfield et al., 2011).

3.2. Data Extraction:

Table 3 shows the extracted data. Data extraction was done to obtain the study name (author and publication year), study design and methodology, the number of probed sites around implants, re-evaluation time points, comparator, reported data (sample

size, number of patients or implants in each group before and after intervention), bleeding on probing scores baseline and final (before and after interventions in test and control groups) and standard deviations.

Chapter 4

Discussion

1. Interpretation and qualitative analysis:

1.1. Interpretation and qualitative analysis of clinical trials:

1.1.1 Anti-infective treatment of peri-implant mucositis: a randomized controlled clinical trial (Heitz-Mayfield et al., 2011):

This clinical study aimed to compare the effectiveness of two anti-infective protocols for the treatment of peri-implant mucositis. Heavy-smoking patients (more than 20 cigarettes/day, patients with poor oral hygiene (full-mouth plaque score more than 25%), patients with untreated periodontitis, and patients with uncontrolled diabetes were excluded. Restoration margins were classified into supra-mucosal or sub-mucosal groups. Twenty nine patients were treated by non-surgical intervention alone or with chlorhexidine gel (0.5%) brushed by patients in the test group (15 patients) twice daily around implant for four weeks. The control group (14 patients) received a placebo gel. Probing depth measurements were assessed using light pressure (0.2-0.3 N) at four sites around implants at baseline, 1 month, and 3 months. No adverse effects were found.

The study reported statistically significant reduction in the mean number of sites with bleeding on probing in both test and control groups at one month compared with baseline measurements. There were no statistically significant differences between test and control groups at one month. There were up to 67% reduction in mean bleeding on probing from baseline to 1 month. At 3 months, 38% of patients had complete resolution of inflammation. Additionally, sub-mucosal restorations showed negative effect on probing depth reduction at 1 month.

They concluded that adding the chlorhexidine gel to mechanical debridement did not enhance the results compared to mechanical cleaning alone. In contrast, implants with supra-mucosal restoration margins showed greater improvements.

1.1.2. Systemic antibiotics and debridement of peri-implant mucositis: A randomized clinical trial (Hallström et al., 2012):

This clinical study was assessing non-surgical debridement with or without systemic azithromycin. Azithromycin can sustain in the inflamed periodontal tissues up to 14 days after systemic administration and has been reported to show clinical and microbiologic improvements (Gomi et al., 2007). Forty-eight patients were treated with non-surgical intervention alone or with systemic antibiotics for 4 days. Only one implant with peri-implant mucositis per patient was chosen. Examiner was blinded to antibiotic administrations. Patients with more than 2 mm bone loss, pregnant, breast feeding,

diabetes mellitus diagnosis, allergic to erythromycin or other macrolides, requiring antibiotic prophylaxis, anti-inflammatory medication usage, taken antibiotics in the past 3 months, and taken medications which affect gingival growth were excluded. Subjects with more than 4 mm pocket depths with bleeding and/or pus on probing were included. The implants' crowns were either cemented or screwed in and they had been restored about 10 years ago. The treatment in both groups included debridement with titanium curettes in addition to polishing by rubber cups and paste, and oral hygiene instructions. In the test group, subjects received 500 mg azithromycin on day 1 and 250 mg on days 2-4. Subjects in the control group did not receive any antibiotic. No adverse effects were reported. Mean bleeding on probing at 4 sites around implant were measured. No statistical differences between the test and control groups were found. They concluded that the clinical improvements might be due to improvements in oral hygiene or the anti-inflammatory effects of azithromycin. Therefore, they found no evidence to recommend systemic antibiotic as an adjunctive treatment.

1.1.3. Effect of a chlorhexidine-containing brush-on gel on peri-implant mucositis (Hallström et al., 2015):

This clinical study was aiming to assess the effect of addition of chlorhexidine gel to mechanical debridement of peri-implant mucositis and oral hygiene instructions. Thirty-eight patients were subjected to either non-surgical intervention alone versus non-surgical intervention in addition to brush on gel chlorhexidine digluconate for 12 weeks. Patients were free of severe medical conditions and were diagnosed with peri-implant

mucositis (bleeding and/or pus on probing with force of 0.2 N). Cases with bone loss more than 2 mm, poorly controlled diabetes, impaired ability to self-performed oral hygiene, and patients taking systemic antibiotics or anti-inflammatory drugs in the past 3 months were excluded. One implant was chosen in each patient. Mechanical debridement was done by titanium curettes and polishing with a rubber cup and paste. Patients in the test group brushed once daily with 1 cm of gel. A 50% reduction in bleeding on probing was regarded as a major improvement. Bleeding on probing was assessed as the primary outcome at four sites around implant. The results were shown as bars with approximate percentages. The chlorhexidine gel resulted in reduced bleeding on probing after 4 and 12 weeks in test group compared to the control group. The probing depths was significantly reduced after 12 weeks in the test group, but not in the control group. They reported moderate but significant improvements of clinical parameters when the treatment was combined with chlorhexidine. No side effects were reported.

2. Statistical Inferences:

The extracted data are presented at table 2. The limited number of high quality studies and the heterogeneity between their protocols and reported data, prevented us from conducting a meta-analysis. These differences were more prominent in reporting the data which prevented further work towards establishing the quantitative consensus of the best evidence. In the study by Heitz-Mayfield and collaborators (2010), the mean number of bleeding on probing positive sites at treated implants, were reported after one

month from the intervention. In the study by Hallström and collaborators (2012), mean bleeding at implants in the control and test groups after one month from the intervention, were reported as percentages with standard deviation. In the study by Hallström and collaborators (2015), bleeding on probing scores after one month from the intervention were reported as approximate percentages shown as statistical bars.

3. Conclusion:

Based on the results of this study, it is difficult to reach a conclusive evidence regarding choosing the best adjunctive option for controlling peri-implant mucositis. Whether it is beneficial to utilize adjunctive methods in addition to mechanical cleaning to treat peri-implant mucositis is still unclear and needs further investigations.

Because peri-implant mucositis is an infectious disease and peri-implantitis which is the more severe form of this disease is difficult to treat, preventive procedures and frequent recalls are called for. Meanwhile, determining the underlying etiological factor is equally important.

On the other hand, adjunctive treatment options such as antibiotics, lasers, and chlorhexidine have their side effects. Chlorhexidine has the disadvantages of taste difference and staining of existing restorations. Although in the retained articles, no side effects were reported, it is important to note that continuing the adjunctive methods for a long period of time might cause possible disadvantages. Even though the photodynamic

alternative was not utilized in the retained articles, cost effectiveness and efficacy of the adjunctive methods are worth to be taken into account. In the study by Hallström and collaborators (2015), the chlorhexidine gel a mild taste and low concentration which might be the reason why no side effects were reported. Chlorhexidine might have the side effects of staining and taste alterations (Frank et al., 2001, Van Strydonck et al., 2012). Another advantage mentioned by this study was that the chlorhexidine application was easy and performed by patients, not professionals (Hallström et al., 2015). In addition, they mentioned that using the chlorhexidine gel reduces the risk of tooth discoloration as opposed to mouthwash (Supranoto et al., 2014).

It was not possible to reach a conclusive evidence regarding the effects of smoking on the results of the intervention. According to the study by Heitz-Mayfield and collaborators (2011), smoking did not show any significant effect on the treatment outcome. However, they noted that this might be due to the few number of smokers (4 patients) in their study and exclusion of the heavy-smokers from their study. In the study by Hallström and collaborators (2015), 65% of patients were smokers and all patients had a history of advanced periodontitis. However, the results were not reported separately for smoker and non-smoker patients. Another interesting fact was that the clinicians and patients were aware of the location of the treatment site which might have resulted in patients' more focused cleaning on that site.

Another important finding of the study by Heitz-Mayfield and collaborators (2011), was that anti-infective protocol did not always result in complete resolution of inflammation. This finding highlights the importance of new approaches in designing the protocol. An

important finding in the study by the Hallström and collaborators (2012) is that the complete resolution of bleeding on probing was only achieved at about 38% of the implants. This finding might highlight the importance of more frequent mechanical cleanings or trying to identify the real etiological factor such as excess cement.

Another important finding in the study by Heitz-Mayfield and collaborators (2011) was that the submucosal restoration margins had a negative effect on this disease and resulted in significantly lower reductions in probing depths after treatment. This finding has been noted in other studies and shows the importance of placing the crown margins above mucosal margins which improves the access for regular cleaning and excess cement cleaning. Additionally, the problems caused by tissue bio-compatibility and possible attachment loss might be reduced (Felton et al., 1991, Lang et al., 1983, Schatzle et al., 2001, Serino et al., 2009, Strub et al., 1978).

In the study be Hallström and collaborators (2012) it was concluded that the clinical improvements might be due to improved oral hygiene. Such improvements would eliminate the formation of calculus in the long term and by itself is an important etiologic factor for peri-implant mucositis. This finding highlights the importance of patient education and motivation. An interesting point was made in the study by the Hallström and collaborators (2015). In their study clinical improvements seemed more pronounced after 4 weeks compared to 12 weeks. This might possibly be due to better oral hygiene of patients in the beginning of the study. Moreover, they inferred that better oral hygiene habits might be more effective than antiseptics.

A new approach to treat peri-implant mucositis is to use probiotics which are living micro-organisms. They might suppress pathogens and increase beneficial host responses. Their anti-microbial effects and anti-inflammatory actions might improve peri-implant mucositis (Teughels et al., 2011). Additionally, probiotics might create a biofilm and protect the oral tissues by occupying the space that the bacteria usually occupy (Caglar et al., 2005, Comelli et al., 2002, Flichy-Fernandez et al., 2015).

4. Implications in improving the clinical health literacy:

Based on the findings of the three retained clinical trials, it seems that focusing on oral hygiene instructions is of utmost importance in maintaining the improvements in peri-implant mucositis. The majority of the patients experienced severe periodontal diseases and tooth loss. Therefore, they were more motivated to maintain their dental implants' health by improving their oral hygiene.

Additionally, frequent recalls and mechanical cleanings might be strongly recommended to avoid the development of a more severe form of peri-implant mucositis, as well as to find any excess cement or to manage other possible etiological factors.

Moreover, educating oral health care providers, hygienists, and patients about this disease would result in faster diagnosis and treatment of this condition. Due to the importance of stopping this disease at initial stages, it is essential to provide information regarding the diagnostic clinical signs of peri-implant mucositis, namely bleeding on

probing, inflamed tissue, and deep pocket depths. Additionally, it is important to educate patients and emphasis on the importance of oral health hygiene.

5. Limitations:

5.1. Study limitations:

Selection bias may have arisen as a result of language restriction to English. Including articles in other languages would provide invaluable information regarding different results in various ethnicities, protocols, and interventions.

Additionally, utilization of limited quality grading instruments could contribute to the presence of bias. For the purpose of this study, CONSORT-2010 checklist was utilized. Other instruments such as CONSORT-10 full questionnaire could also be utilized.

Moreover, the limited number of acceptable studies prevented the possibility of conducting a meta-analysis. Few studies have assessed or reported their results after 4-6 weeks of intervention. This factor was one of the main reasons for the limited number of articles.

Finally, there are other existing methods to evaluate the inflammation, namely pocket depth and plaque index reductions which were not included in this study.

5.2. Field limitations:

Bleeding on probing occurrence partly depends on the pressure applied by the clinician. The expected pressure is supposed to be about 0.25 Ncm which does not damage the mucosa. This clinical parameter is considered an important diagnostic tool for peri-implant mucositis (Etter et al., 2002, Lang et al., 1994, Schou et al., 2002). It would be difficult to standardize this pressure between different clinicians or even for the same clinician at different times. While this issue can be partially solved by training the clinicians before the study, these differences might alter the reported results.

Additionally, studies utilized heterogeneous protocols. While some studies assessed bleeding on probing at four sites around implants, others decided to examine this factor at six points. Besides, some studies looked at full-mouth bleeding on probing scores instead of bleeding on probing scores only around implants.

Moreover, different studies assessed the interventions' results at different time points. Most studies did not evaluate patients within 4-6 weeks of intervention which leads to an increased chance of interferences of other factors such as poor oral hygiene in the reported results.

While some studies assessed smoking and diabetic patients separately, others included them in the same group as the non-diabetic or non-smoker patients. It would have been very beneficial if the results were reported for each group separately to provide a chance to compare the differences and to better understand the effect of smoking and diabetes on

the intervention results.

Finally, some studies reported the number of implants while others reported the number of patients for their studies' sample sizes. Ideally, one implant in each patient would be considered, which matches the treatment and control groups better. However, some studies included different numbers of implants of each patient in their studies.

Tables

Table (1): Clinical trials grading scores (CONSORT10 Checklist)

CONSORT10 Qs	1a	1b	2a	2b	3a	3b	4a	4b	5	6a	6b	7a	7b	8a	8b	9	10	11a	11b	12a	12b
Clinical Trials																					
Hallström et al., 2012	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	1	2	1
Porras et al., 2002	1	2	2	2	2	1	2	2	2	2	1	1	1	1	1	1	1	2	1	2	1
Thöne et al., 2009	1	2	2	2	2	1	2	2	2	2	1	1	1	2	1	2	2	1	1	2	1
Heitz et al., 2011	2	2	2	2	1	1	2	2	2	2	1	2	2	2	2	2	1	2	1	2	2
Hallström et al., 2015	1	2	2	2	2	1	2	2	2	2	1	2	1	2	2	2	2	2	1	2	1

CONSORT10	13a	13b	14a	14b	15	16	17a	17b	18	19	20	21	22	23	24	25	Total
Clinical Trials																	
Hallström et al., 2012	2	2	2	1	2	2	2	1	1	1	1	2	2	1	1	1	62
Porras et al., 2002	2	1	2	1	2	2	1	1	1	1	2	2	2	1	1	1	54
Thöne et al., 2009	2	1	2	1	2	2	2	1	1	1	2	1	2	1	1	1	56
Heitz et al., 2011	2	1	2	1	2	2	2	1	1	1	1	2	2	1	1	2	61
Hallström et al., 2015	2	2	2	1	1	2	2	1	1	2	2	2	2	1	1	2	62

Table (2): Extracted data

Author and publication year)	Study design	Sample size	Intervention	Comparator	Assessment time points	Method of assessment	Bop baseline in control group	SD
Hallström et al., 2012	Randomized clinical trial	48	Mechanical debridement	Mechanical debridement plus antibiotics	1 month	Mean bleeding on probing%	80.0	25.0
Heitz et al., 2011	Randomized clinical trial	29	Mechanical debridement	Mechanical debridement plus Chlorhexidine gel	1 month	Mean number of bleeding on probing positive sites	2.3	1.0
Hallström et al., 2015	Randomized clinical trial	38	Mechanical debridement	Mechanical debridement plus Chlorhexidine gel	1 month	Bleeding on probing%	56	

Author and publication year)	BOP after intervention in control group	SD	Bop baseline in test group	SD	BOP after intervention in test group	SD
Hallström et al., 2012	54.2	31.9	82.6	24.4	38.0	23.7
Heitz et al., 2011	1.0	1.0	2.5	1.0	1.2	0.9
Hallström et al., 2015	46		48		13	

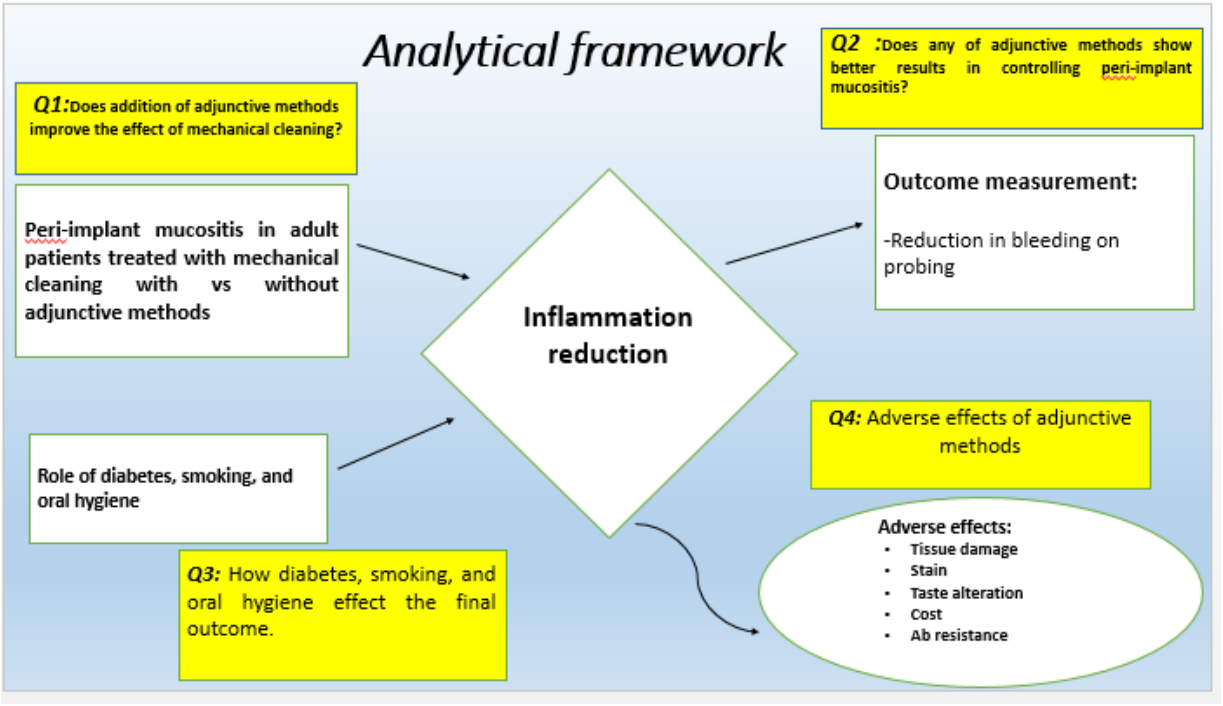

Figure 1 presents the analytic framework. The analytic framework represents relevant clinical concepts and refines the relationship between outcome measures and health outcomes. It helps to understand clinical decisions. The following key questions are included in the analytical framework and are shown in yellow rectangles:

1. Does addition of adjunctive methods improve the effect of mechanical cleaning?

2. Does any of adjunctive methods show better results in controlling peri-implant mucositis compared to the rest?

3. How do diabetes, smoking, and oral hygiene effect the final outcome?

4. What are the possible adverse effects of adjunctive methods?

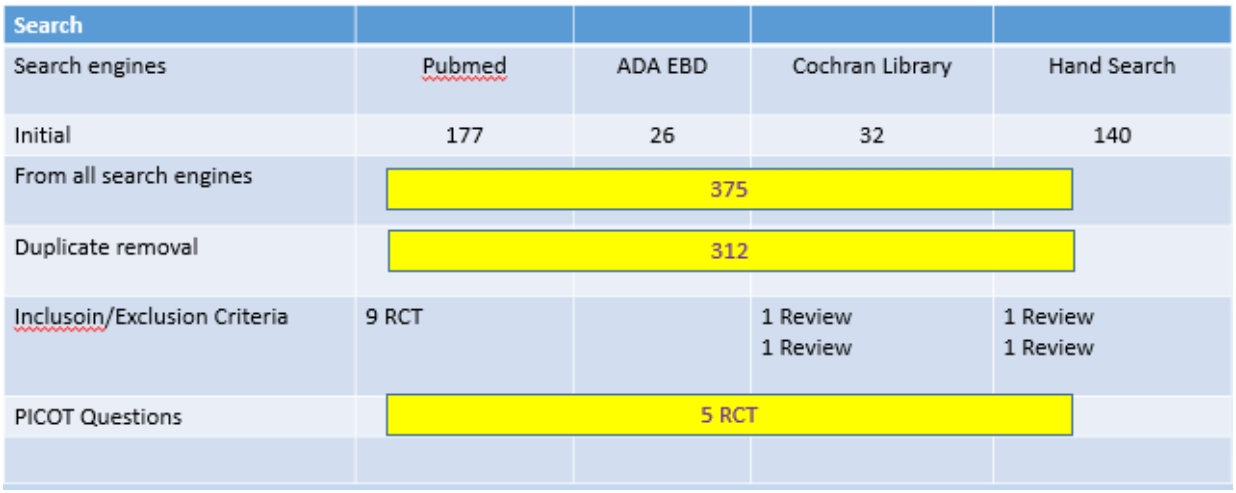

Figure 2 is presenting a summary of randomized clinical trials selection process. The following search engines were explored: PubMed, Cochrane library, American Dental Association web library. The relevance of the identified systematic reviews and clinical trials to the study and PICOTS questions was assessed. The PICOTS questions were applied to the methodology and results of each study to filter papers after applying the inclusion and exclusion criteria and to determine the faithfulness of each identified paper in the bibliome.

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