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Title: Treatment of peri-implantitis: clinical comparison between conventional treatment versus conventional plus Biolase laser treatment as a co-adjuvant
Protocol: AAAR8727
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Study Purpose and Rationale

With advances to implant dentistry over the past several decades, endosseous implants have become more prevalent in the population as an effective means of restoring function to edentulous areas. The use of dental implants has transformed the dental landscape and has dramatically altered the way clinicians treat edentulous and partially edentulous patients. As the number of implants is on the rise, the prevalence of disease around existing dental implants has become more widespread. Peri-implantitis has been defined as the presence of destructive soft tissue inflammation leading to pocket formation and bone loss around an osseointegrated implant (Albrektsson T, 1994). The presence of peri-implantitis has been estimated to be between 28-56% of patients and 12-40% of implants (Zitzmann N, 2008). The widespread presence of peri-implantitis has led to numerous attempts to manage and treat a disease which currently has no standardized protocol. Many methods at attempting to control the inflammatory process around implants have been attempted. In cases of peri-mucositis in animal studies, non-surgical therapy utilizing mechanical debridement has been shown to reduce inflammation (Trejo P, 2006). Non-surgical debridement of the implant is often the first line of defense, along with oral hygiene instruction, to prevent cases of peri-mucositis to progress to pocket formation and bone loss. Chlorhexidine rinses (Felo A, 1997) and both systemic (Mombelli A, 1992) and local (Büchter A, 2004) treatment with antibiotics have also been used as adjunctive therapy with varying results. Non-surgical therapy of peri-implantitis cases has not shown, however, to produce predictable results in terms of pocket reduction and reduced inflammation in the long term (Renvert S, 2008). Eventually, surgical intervention for cases of significant pocketing was also attempted around dental implants. The Cumulative Interceptive Supportive Therapy (CIST) protocol was developed out of these previous findings.

Systematic reviewers have suggested that combining several non-surgical therapies together for mild cases and surgical intervention for severe cases appears to be the most effective method of approaching peri-implantitis (Klinge B, 2002). The CIST protocol recommends mechanical debridement for cases with no attachment loss around an implant, which are essentially mucositis cases. When pocket depths approach 4-5 mm, antiseptic cleansing is recommended as an addition to mechanical debridement. When minor bone loss of less than 2 mm is detected as well, systemic or local antibiotic therapy is then administered. When the amount of bone loss exceeds 2 mm, the protocol then recommends resective or regenerative surgery in the site (Lang N, 2004). Relatively recently, the use of lasers for treatment of peri-implantitis has shown promising results across a variety of laser systems. Various authors have published cases utilizing CO2, diode, Er,Cr:YSGG, Er:YAG, and Nd:YAG lasers to treat peri-implantitis. Currently, the use of lasers provides a mean to remove the bacterial challenge on the surface of titanium implants. Er,Cr:YSGG in peri-implantitis cases has shown reduced pocket depths and bleeding on probing (Al-Falaki R , 2014). In another case report, Er,Cr:YSGG has improved pocket depth, bleeding, implant mobility, and bone formation around implant (Azeeh M , 2008). Er,Cr:YSGG seems efficient in removing contaminants on roughened implant surface with no effects on titanium substrate under electronic microscope examination (Miller R , 2004). Schwarz has several studies using the Er:YAG laser and have shown that decontamination of the implant surface is possible through his methods as well, although there is no definitive protocol and efficacy of its usage (Schwarz F, 2006). Furthermore, in a study using diode lasers for the treatment of peri-implantitis, Lerario showed a significant reduction in probing depth in patients treated with a diode laser compared to those treated with standard scaling and root planing (Lerario F, 2016) while one formation was evident in one peri-implantitis case treated with Er,Cr:YSGG (Zuhair S , 2015). These promising results promote the need to conduct additional studies that elucidate the efficacy of utilizing lasers in the treatment of peri-implantits as very few studies have been shown comparing the use of lasers as a means to sanitize the surface of the implant in comparison

to other methods in a randomized, controlled environment. As mentioned, previous studies verify that decontamination of the implant surface is very successful with the use of lasers, and this area of implant dentistry warrants further exploration. The aim of this study is to explore the clinical effects of treating ailing implants non-surgically with the Er,Cr:YSGG laser, and compare the results to traditional methods of non-surgical therapy.

References: Albrektsson T, I. F. (1994). Consensus report of session IV. Proceedings of the 1st European Workshop on Periodontology., 365-369. Al-Falaki R , M. F. (2014) Treatment outcome following use of the erbium, chromium:yttrium, scandium, gallium, garnet laser in the non-surgical management of peri-implantitis: a case series British Dental Journal Volume 217. 453-457. Azzeh M. (2008) Er,Cr:YSGG Laser-Assisted Surgical Treatment of Peri-Implantitis With 1-Year Reentry and 18- Month Follow-Up. J Periodontol. 2000-2005. Büchter A, M. U.-L. (2004). Sustained release of doxycycline for the treatment of peri-implantitis: randomised controlled trial. British Journal of Oral and Maxillofacial Surgery, 439-444.Felo A, S. O. (1997). Effects of subgingival chlorhexidine irrigation on peri-implant maintenance. American Journal of Dentistry, 107-110. Klinge B, G. A. (2002). A sytemic review of the effect of anti-infective therapy in the treatment of peri-implantitis. Journal of Clinical Periodontology, 213-225. Lang N, B. T.-M. (2004). Consensus Statements and Recommended Clinical Procedures Regarding Implant Survival and Complications. The International Journal of Oral and Maxillofacial Implants, 150-154. Lerario, Francesco, et al. "Non-surgical periodontal treatment of peri-implant diseases with the adjunctive use of diode laser: preliminary clinical study." Lasers in medical science 31.1 (2016): 1-6. Miller R. (2004) Treatment of the Contaminated Implant Surface Using the Er,Cr:YSGG Laser. Implant Dentistry / Volume 13, Number 2. 165-170. Mombelli A, L. N. (1992). Antimicrobial treatment of peri-implant infections. Clinical Oral Implants Research, 162-168.Renvert S, R.-J. A. (2008). Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review. Journal of Clinical Periodontology, 305-315. Schwarz F, B. K. (2006). Clinical and histological healing pattern of peri-implantitis lesions following non-surgical treatment with an Er:YAG laser. Lasers in Surgery and Medicine, 663-671. Trejo P, B. G. (2006). Effect of mechanical and antiseptic therapy on peri-implant mucositis: an experimental study in monkeys. Clinical Oral Implants Research, 294-304. Zitzmann N, B. T. (2008). Definition and prevalence of peri-implant diseases. Journal of Clinical Periodontology, 286-291. Zuhair S, A. L. W. (2004) Comparison of the Efficacy of Different Types of Laser for the Treatment of Peri-Implantitis: A systematic Review. Int J Oral Maxillofacial Implant. 339-345.

Study Design

This clinical study will involve 26 human subjects pre-screened at Columbia University with the presence of at least one implant presenting with early to moderate peri-implantitis. Peri-implantitis has been defined as an implant restoration with inflamed bleeding gingiva, probing depths around the implant of 5- 8mm, bone loss and exposure of threads around the implant (limited to one-third of the threads exposed). The purpose of this study is to determine the benefits of treating peri-implantitis with a closed laser approach known as the “Repair Protocol” using an Er,Cr:YSGG laser compared with traditional non-surgical therapy. Each subject, when determined to fall under the parameters of the study for peri-implantitis, will be randomly assigned to one of two groups: the test Er,Cr:YSGG laser group or the control group. The study will constitute a human double-blind randomized clinical trial in which both examiners and patients will be blinded to the treatment. In order to ensure the blinding of the patients, the laser will be applied to all implants, although it will not be activated in the control group. The therapist will be the same person throughout the study while the examiners will be calibrated. The two groups that will constitute the study and the procedures that will be applied are:

Experimental: Scaling and root planning with an ultrasonic or piezoelectric instrument and hand instrumentation with hand instruments. No prosthetic components will be removed. Application of laser therapy following the specifics of the company.

Control: Scaling and root planning with an ultrasonic or piezoelectric instrument and hand instrumentation with hand instruments. A sham, inactivated laser, treatment will be delivered.

Data to be collected include: Primary outcome measures will include: presence of bleeding on probing, probing depth, and the progression of bone loss around the implant, as measured with bone sounding under local anesthesia and radiographically with the aid of a stent. Secondary outcome measures will include: Gingival index (GI), Plaque Index, mobility, and suppuration.

Statistical Procedures

Power calculation was done based on a study published by Lerario et al., 2016. To detect a difference of 1.72 mm (SD: 1.13mm) in probing depth at 9 months of follow-up after the use of Er,Cr: YSGG laser therapy we will need 13 patients in each of control and test groups (at 90% power, and alpha of 0.05). The ratio of sample size in group 1 to group 2 is 1.

Confidentiality

The study data will be recorded on paper during the appointments and will be transferred electronically to an encrypted computer designated for the study. The paper copy will only be seen and handled by the primary provider. When the data is transferred electronically, the hard copy will be destroyed. The excel files will only be located on encrypted laptops and desktops designated for the study. The data will be coded once it becomes electronic, and only the study team will have access to the identifiable data.

Limitations of compelled disclosure and mandatory reporting apply, and only during these special circumstances will the identities be disclosed.

Participants will only be seen by faculty and students participating in the study. During analysis of the data, patients will not be identified by name, only by a designated number identifying the patient in the health record software (coded). Only members of the study team will have access to the identifiable data.

Study Procedures

On the day of treatment, each subject will be randomly assigned to either the control group or the treatment group (envelopes with the respective groups will be prepared and drawn at the day of treatment). All ailing implants will be left closed with no incisions or flaps made to expose the implant surface surgically. Prior to treatment, radiographs will be taken utilizing a radiographic stent utilizing bite registration impression material, which will be stored for the final radiograph at the end of the study for standardization. In addition, gingival bleeding, recession, loss of attachment and tissue type will be recorded. All subjects receiving treatment will then be anesthetized with 2% lidocaine with 1:100,000 epinephrine, utilizing only buccal and palatal infiltrations with no interpapillary injections. The implant will be sounded with a periodontal probe to measure bone levels at four sites.

In the control group, the implants will be debrided with curettes and ultrasonic scaler with standard tips. No prosthetic components will be removed in this study. The occlusion of the restorations supported by the ailing implant will be evaluated, and all balancing contacts, heavy occlusion, and excessive marginal ridge contacts will be removed.

In the Er,Cr:YSGG laser test group, the Er,Cr:YSGG laser will then be used to irradiate the implant surface utilizing a closed technique. The “Repair Protocol” will be utilized on the experimental implants. The “Repair Protocol" consists of several steps including but not limited to the following: Outer Pocket De-Epithelialization, Gingivectomy (as needed), De-Epithelialization and Retraction, Scaling and Root planing, Sulcular Debridement/Degranulation, Bone Decortication, Final Sulcular Debridement, and Compression with a wet 2X2. Occlusal adjustment will also be done at the conclusion of the procedure identical to the control group.

Oral hygiene instructions will be given to all patients after treatment.

Subjects will return for 1-week, 3-month, 6-month & 9-month evaluations. At the initial and the 9-month visits, the implant will be assessed for bleeding on probing, probing depths at four sites around the implant, clinical attachment level, and recession. Standardized radiographs will be taken at baseline and at the end of study at 9 months. At every recall visit, only supragingival polishing will be completed without the use of curettes or periodontal probes. At 9 months, the patient will receive a final evaluation for the study.

Medical Device

Device name: WaterLase iPlus
Device description: Er, Cr:YSGG laser
Device Model/Version #: WaterLase iPlus
Phase of Study: Feasibility
Manufacturer: Biolase Technology, Inc.

Recruitment

Participants will be currently enrolled patients being seen at Columbia University College of Dental Medicine. Patients at Columbia University will have already completed written consent to be treated at the University for dental care. Participants of the study will be approached by their current dental provider and if they agree, then they will be brought into contact with the research team. Alternatively, the treating dentist may provide information about the study along with contact information for the researchers, so the patients may contact the researchers if they are interested in participating. If the patient shows interest, he or she will have an interview with the Principal Investigator or other investigators to discuss the details of patient involvement and the potential risk and complications derived from the participation in the study. Written consent will be obtained prior to treatment and induction into the study on a day prior to rendering treatment for the study itself.

Research Question(s)/Hypothesis(es)

The purpose of the study is to observe the effects of two commonly utilized treatment modalities for peri-implantitis and to compare the results. The first method of treatment is debridement with curettes and ultrasonic scalers and it represents the traditional approach in the treatment of peri-implantitis. The

second method of treatment involves the use of the Biolase laser in addition to the traditional approach of debriding with curettes and ultrasonic scalers. No studies exist comparing these two approaches, and this will serve as a pilot study to explore possible differences. Our research hypothesis is that the addition of Er;Cr;YSGG laser is likely to be more effective in removing the microbiota from a rough implant surface, and that this will manifest with improved clinical parameters in subjects that receive this method of treatment.

Scientific Abstract

With advances to implant dentistry over the past several decades, endosseous implants have become more prevalent in the population as an effective means of restoring function to edentulous areas. The use of dental implants has transformed the dental landscape and has dramatically altered the way clinicians treat edentulous and partially edentulous patients. As the number of implants is on the rise, the prevalence of disease around existing dental implants has become more widespread. Peri-implantitis has been defined as the presence of destructive soft tissue inflammation leading to pocket formation and bone loss around an osseointegrated implant (Albrektsson T, 1994) . The presence of peri-implantitis has been estimated to be between 28-56% of patients and 12-40% of implants (Zitzmann N, 2008). The widespread presence of peri-implantitis has led to numerous attempts to manage and treat a disease which currently has no standardized protocol. Many methods at attempting to control the inflammatory process around implants have been attempted. In cases of peri-mucositis in animal studies, non-surgical therapy utilizing mechanical debridement has been shown to reduce inflammation (Trejo P, 2006). Non-surgical debridement of the implant is often the first line of defense, along with oral hygiene instruction, to prevent cases of peri-mucositis to progress to pocket formation and bone loss. Chlorhexidine rinses (Felo A, 1997) and both systemic (Mombelli A, 1992) and local (Büchter A, 2004) treatment with antibiotics have also been used as adjunctive therapy with varying results. Non-surgical therapy of peri-implantitis cases has not shown, however, to produce predictable results in terms of pocket reduction and reduced inflammation in the long term (Renvert S, 2008). Eventually, surgical intervention for cases of significant pocketing was also attempted around dental implants. The Cumulative Interceptive Supportive Therapy (CIST) protocol was developed out of these previous findings. Systematic reviewers have suggested that combining several non-surgical therapies together for mild cases and surgical intervention for severe cases appears to be the most effective method of approaching peri-implantitis (Klinge B, 2002). The CIST protocol recommends mechanical debridement for cases with no attachment loss around an implant, which are essentially mucositis cases. When pocket depths approach 4-5 mm, antiseptic cleansing is recommended as an addition to mechanical debridement. When minor bone loss of less than 2 mm is detected as well, systemic or local antibiotic therapy is then administered. When the amount of bone loss exceeds 2 mm, the protocol then recommends respective or regenerative surgery in the site (Lang N, 2004).Relatively recently, the use of lasers for treatment of peri-implantitis has shown promising results across a variety of laser systems. Various authors have published cases utilizing Er,Cr:YSGG, Er:YAG, Nd:YAG, and CO2 lasers to treat peri-implantitis. Currently, the use of lasers provides a means to remove the bacterial challenge on the surface of titanium implants. Er,Cr:YSGG in peri-implantitis cases has shown reduced pocket depths and bleeding on probing (Al-Falaki R , 2014). In another case report, Er,Cr:YSGG has improved pocket depth, bleeding, implant mobility, and bone formation around implants (Azeeh M, 2008). The Er,Cr:YSGG seems efficient in removing contaminants on roughened implant surface with no effects on titanium substrate under electronic microscope examination (Miller R, 2004, Linden E, 2017 to be published). Bone formation was evident in one peri-implantitis case treated with Er,Cr:YSGG (Zuhair S , 2015).Schwarz has several studies using the Er:YAG laser and have shown that decontamination of the implant surface is possible through his methods as well, although there is no definitive protocol and efficacy of its usage

(Schwarz F, 2006) .Very few studies have been shown comparing the use of lasers as a means to sanitize the surface of the implant in comparison to other methods in a randomized, controlled environment. Previous studies verify that decontamination of the implant surface is very successful with the use of lasers, and this area of implant dentistry warrants further exploration. The aim of this study will be to explore the clinical effects of treating ailing implants non-surgically with the Er,Cr:YSGG laser, and compare the results to traditional methods of non-surgical therapy utilizing scalers and chlorhexidine rinses. This experiment will involve 26 human subjects pre-screened at Columbia University with the presence of peri-implantitis, which has been defined as an implant restoration with inflamed bleeding gingiva, bone loss and exposure of threads around the implant. This human clinical trial will utilize early to moderate peri-implantitis with no more than one third of threads exposed. The purpose of this study is to determine the benefits of treating peri-implantitis with a closed laser approach known as the "Repair Protocol" using an Er,Cr:YSGG laser compared with traditional non-surgical therapy. Each subject, when determined to fall under the parameters of the study for peri-implantitis, will be randomly assigned to one of two groups: the test Er,Cr:YSGG laser group or the control group. Primary outcome measures will be the presence of bleeding on probing, gingival index and the progression of bone loss around the implant, as measured with bone sounding under local anesthesia and radiographically with the aid of a standardized stent.

Lay Abstract

Dental implants are becoming more and more popular as a means to replace missing teeth. As more dental implants are being placed each year, clinicians are facing the challenges of common causes for failure or compromise of these dental implants. Gum disease, which has plagued natural teeth for many years, can manifest on dental implants in the form of a disease known as peri-implantitis. Peri-implantitis occurs when the presence of bacteria leads to inflammation of the area, and can be the reason for loss of bone around implants. Currently, there is no standard method for treating peri-implantitis. There are several common methods for treating this disease. One method involves cleaning off the implant with scalers in a manner similar to teeth during cleanings. The other method utilizes the same method and adds the use of a laser to remove most of the bacteria from the surface of the implant. In this study, we would like to compare these two methods and see if there is any additional benefit from using the laser technology. The goal is to determine which method is more effective at arresting the progression of peri-implantitis. For this means, we will be taking clinical measurements and X-rays. This will allow us to determine the status of the implant, improvement in the inflammation and changes in bone level. The implants will be treated at the baseline and checked during the follow-up appointments with the last appointment provided at the 9 months.

Risks, Benefits, Alternatives

The risk involved with the laser debridement directly to the patient is minimal. Potential risks may be postoperative infection or soft tissue trauma. The procedure is a conservative surgery-free debridement of the implant with the Biolase laser, and there is very little risk of having postoperative complications. Proper protocol for laser safety will be followed when utilizing the Biolase laser. Both procedures involved with the study are the standard of care for treatment.

Risks and complications of the use of lasers involve: eye and skin damage, thermal damage of the tissues and the adjacent structures, alterations of the implant, restorations of other surfaces, damage of critical structures (i.e. nerves and vessels), embolism, water splashing and rupture of the tip of the laser.

The benefits of the study with enrolled patients is that they are able to receive treatment on ailing implants, whether through non-surgical means or with use of the laser. There is no compensation for the study, since it utilizes therapy that the patient would have needed regardless of participation. Currently, because no standardized protocol exists for the treatment of peri-implantitis, the benefit of this study will be to help collect data on treatment methods to gain additional knowledge on the most optimal treatment methods for peri-implantitis. This is an area that has very little conclusive evidence in terms of treatment modalities that are most effective, and more information is needed to determine the most effective way to treat peri-implantitis.

The alternative intervention for the subject is to not participate in the study and have the implant treated outside the study.

Data and Safety Monitoring

The data will be recorded on paper when the patient is seen by the operator. The study data will then be stored in an Excel file on an encrypted desktop or laptop computer immediately after the encounter with the patient. The paper documents used to collect data will then be destroyed once recorded electronically. There is minimal risk, and therefore there will be no data and safety monitoring board involved. The measurements will also be recorded in the electronic database for every patient (Axium) as a part of their dental treatment records.

The readings for gingival bleeding, periodontal probing, and attachment loss will be monitored for each patient at every visit and compared with previous readings for every patient. Monitoring for any unexpected outcomes, such as a severe increase in attachment loss/probing or gingival inflammation, will be completed after every visit with a patient for study purposes. Any patient showing aberrant findings and potential high risk for the study treatment will be identified and reported to the IRB. All investigators will be tasked with the data and safety monitoring for all patients.