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EFFECT OF ND:YAG LASER THERAPY AS AN ADJUNCTIVE IN THE TREATMENT OF CHRONIC PERIODONTITIS, SYSTEMATIC REVIEW.

[Document subtitle]

A thesis submitted in fulfillment of the requirements for the degree of Master of Science in Medical Research Methodology

By

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LIST OF ABBREVIATIONS
Main list:
CP: Chronic Periodontist.
PD: Periodontal Disease.
PI: Plaque Index.
BOP: Bleeding on Probing.
PPD: Periodontal Probing Depth.
CAL: Attachment Level Gain.
CI: Confidence Intervals.
SD: Standard Deviation.
MD: Mean Difference.
IV: Inversive Variance.
M: Mean value.
N: Number of Participants.
SRP: Sealing and Root Planning.
Nd: YAG: eodynamium-doped yttrium aluminum garnet;Nd:Y₃Al₅O₁₂

mm: millimeter.
nm: nanometer.
mj: millijoules.
ms: milliseconds.
Hz: Hertz.
ks: milliseconds.

Studies:
1- Eltas 2012
2- Eltas November 2012
3- Gomez 2011
4- Javed 2016
5- Qadri 2010
6- Slot 2011
ABSTRACT

Context: the covenantal scaling and root planing (SRP) has been used for the treatment of chronic periodontitis but due to the different limitations of this therapeutic method it lead to develop new treatments strategies like Nd:YAG laser. However, the effectiveness of this kind of laser in periodontal treatment remains ambiguous.

Objective: The aim of this systematic review was to assess the effects of Nd:YAG laser therapy as an adjunctive to scaling and root planing (SRP) in the treatment of chronic periodontitis in comparison to SRP alone or with placebo.

Data Sources: Electronic bibliographic database were searched, MEDLINE, EMBASE, CENTRAL ,Clinical trials(WHO) , Eu clinical trials and other databases. 429 references imported for screening and 200 duplicates removed. while 229 studies screened against title and abstract, and 192 studies excluded 37 studies assessed for full-text eligibility and 31 studies excluded. Finally 6 studies were included in Meta-analysis.

Eligability criteria: The inclusion criteria are patients diagnosed with Chronic Periodontitis, randomized controlled studies(RCTs), adult participants (age ≥ year-old). While the exclusion criteria are the following: studies that compared SRP with Nd:YAG laser versus SRP alone or placebo articles in English, patients who have a systematic disease that could influence the periodontal tissues, pregnant women, people who consume medicine that is known for its effect on periodontal disease or treatment.reports that did not analyze the primary outcomes, and periodontal therapy that has done the last six months.
Conclusion: The results for this systematic review and meta-analysis found no evidence of the effectiveness of Nd:YAG laser utilized as an adjunctive compared to SRP alone in the treatment of chronic periodontitis.

INTRODUCTION

Context:
Periodontitis is inflammation that affects the soft tissue and periodontium, the periodontium consists of the gingiva, cementum, periodontal ligament, alveolar mucosa and the alveolar bone (Palumbo, 2011). These tissues surround the tooth and serve in maintaining it in the alveolar bone, which is part of the maxilla and the mandible. The inflammatory processes cause slowly and progressively destruction of the periodontal attachment structures and if it left untreated will eventually lead to losing the tooth.

Periodontal disease is one of the most common oral condition of the population and it represents important oral health worldwide. it is highly prevalent in developed and developing countries, it affects about 20-50% of the population around the world (Nazir, 2017).

Periodontitis caused by specific microorganisms that exist in the oral cavity

Another new therapy is the use of different types of lasers such as Neodymium-doped: yttrium, aluminum, and garnet (Nd: YAG) laser therapy with SRP.

Nd: YAG is one kind of solid-state laser emitting light at a 1064nm wavelength and has low absorption in water. It has various characteristics such as hemostasis, ablation, sterilization, and bactericidal effects.

In 1997, the application of Nd: YAG laser has been approved by FDA for soft tissue curettage and surgery, sulcular debridement and caries removing. Laser treatment is
considered as a nonsurgical therapy, due to successfully use it for soft tissue application without anesthesia and with minimal bleeding.

In periodontology, Nd: YAG laser has been used for pocket curettage because of their flexible fiber delivery system which is suitable for pocket insertion. It can be an alternative or an adjunct to conventional mechanical therapy of periodontal diseases.

Nd:YAG is a material, more specifically, a crystal, that is used as a lasing material in laser machines. Nd:YAG is a solid state laser, considered as a 4 level laser. The first successful laser operation was achieved in 1960 by Theodore Maiman, which by this achievement, opened the lock to the discovery of many other types of lasers, such as gas, liquid, solid and semiconductor lasers. One year later, On the December of 1961, Elias Snitzer, a scientist, first discovered in 1961 that the laser action in barium crown glass doped with neodymium ions.

His work won the admiration of other scientists, and they are Geusic, Marcos, and Van Uitere. His work led them to announce the creation of the Nd: YAG laser in 1964, along with laser action in other neodymium doped garnets.

The laser therapy has bactericidal and detoxification effects, it can remove epithelialliming, granulation tissue, plaque and calculus within the periodontal pockets with low mechanical stress and without leaving a smear layer on root surfaces. There are many advantages of the laser treatment in dentistry, some of them are the following:

1- Minimizing cellular destruction and tissue swelling.
2- Increasing the visualization of surgical locations, and reduces pain.
3- It helps in hemostasis.
Nd: YAG laser has the frequency of 20 Hz, with 2 Watts, has the speed of 50/100 ks and 100 MJ.

Nd: YAG laser has been widely used in medicine. For example, it is used in many surgeries by the Ophthalmologist, oncologists, dentists, podiatrists, as well as in the cosmetic field, and many more.

In Dentistry, the dental lasers are used for soft tissue surgeries in the oral cavity, such as periodontal sulcular debridement, gingivectomy, biopsy, pulpotomy LANAP, frenectomy, and coagulation of graft donor sites.

These lasers are widely known for its use in periodontal treatment, their tendency for pigment tissue for effective debridement and disinfection of periodontal pockets. Moreover, it decontaminates the bacteria in tissues, also contributes in the treatment of periodontal Infection.

The periodontal treatment procedure is done by the following steps:
- Scaling and root planning (SRP)
- Local antiseptic
- Systematic antibiotic administrative
- Extraction.

The carbon dioxide laser has been known for its use in soft tissue surgeries, while the Nd:YAG laser is used in both soft and hard tissue surgeries.

The benefits of the Nd: YAG laser in dentistry, other than its benefits in Gingivectomy, GINGIVOPLASTY, Operculectomy, and in biopsy, is has many other advantages, such as:
- it cuts the draining procedure, and treats aphthous ulcers.

At time passes by, and many scientific investigations expand, it is expected that the dental Nd:YAG laser to develop even more in new dental adhesives and composite systems, more methods in managing caries and new treatments for endodontic. Which is having a positive impact on patients, as well as a positive impact to the dentists who are using this laser.
OBJECTIVES

The aim of this systematic review was to assess the effects of Nd: YAG laser therapy as an adjunctive to scaling and root planing (SRP) in the treatment of chronic periodontitis in comparison to SRP alone or with placebo.

Thus, we evaluated scientific evidence regarding clinical efficacy in terms of reduction in periodontal pockets, gain of clinical attachment level and reducing of inflammation in population with moderate chronic periodontitis.

MATERIALS AND METHODS

This systematic review was accomplished according to PRISMA guidelines (the Preferred Reporting Items for Systematic Review) (Liberati et al., 2009) and the Cochrane Collaboration guidelines (Higgins JPT, 2011).

Protocol:

The rational, hypothesis, exclusion and inclusion criteria, methods of analysis and outcomes of primary and secondary interest of this systematic review were specified and documented in advance in a protocol. The protocol was developed according to PRISMA-P statement (Preferred reporting items for systematic review and meta-analysis protocols, 2015 statement) (Moher et al., 2015).

Eligibility criteria:

Studies were selected according to the criteria outlined below,
1. Populations/Participants:

We included studies that examined adult population (18 years old and more), they have to be free from systematic disease/conditions and have been diagnosed with chronic periodontitis. The definition of chronic periodontist was adopted from the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions (Wiebe, 2000).

We excluded studies including participants/people with the following conditions:

- People who take any medication known for its effects on periodontal disease or treatment in the last three months.
- Pregnant women.
- Systematic diseases such as HIV (Groenewegen et al., 2018), Cancer, Diabetes (Preshaw et al., 2012) and other.
- People underwent chemotherapy or actinotherapy.
- Necrotizing periodontitis.
- Recurrent periodontitis.
- Periodontitis as a manifestation of systematic diseases.

2. Interventions:

In the included study the intervention of interest is the use of Nd: YAG laser in the treatment of periodontal disease as an adjunctive to scaling and root planning (SRP) in comparison with SPR alone or placebo. The selected studies must describe the phase of periodontal treatment, whether it is untreated or in the maintenance period.

Exclusion criteria:

- Studies comparing the use of Nd: YAG laser alone versus SPR with Nd:YAG.
• Studies using antimicrobials/ antibiotics with SPR.

• Studies using other kinds of a laser such as Er:YAG laser comparing it with SRP.

3. Comparator:
We compared Nd:YAG laser as an adjunctive to scaling and root planing (SRP) with SPR alone or with placebo.

Exclusion criteria:
• Studies comparing the use of Nd: YAG laser alone versus SPR with Nd:YAG.
• Studies using other kinds of a laser such as Er: YAG laser comparing it with SRP.

4. Outcomes:

**Primary outcomes:**
Changing in probing pocket depth (PPD) (mm) from baseline to end of the study.
Varying in clinical attachment level (CAL) (mm) from baseline to end of the study.
Changing in Plaque index (PI) from baseline to end of the study.

**Secondary outcomes:**
Modifying in bleeding on probing (BOP) (%) from baseline to end of the study.
Changing in microbial counts (counts) from baseline to end of the study.

The timing of outcomes measurements: We will consider a short-term outcome for up to six months and long-term outcome for above six months.

5. Study design:
We included randomized controlled studies (RCTs) in this Systematic review.

**Sources and search strategy:**

the following major electronics bibliographic databases from 1990 to 9/5/2018, Medline( from US National Library of Medicine), EMBASE(Elsevier ), Evidence-Based Dentistry (EBD), Web of Science and CENTRAL trials registry of the Cochrane Collaboration, and other like Google Scholar database were searched by a an individual.

Furthermore, I searched grey literature, abstracts of conferences and meeting as well as, the ClinicalTrials.gov, the International Clinical Trials Registry Platform Search Portal(WHO, no date) (ICTRP), ISRCTN registry (UK), EASD virtual meeting and Eu Clinical Trials were searched for ongoing and recently completed trials. Furthermore, PROSPERO was searched for ongoing and recently completed systematic reviews.

Finally, we searched for unpublished articles in the following scientific journals,

- Journal of Periodontology
- Journal of Periodontal Research
- Clinical Oral Investigations
- Journal of Laser Dentistry
- International Journal of Laser Dentistry
- Journal of Dental Laser
- Journal of Dental Research
- Journal of Dental Science
- Lasers in Medical Science
- The Journal of American Dental Association (JADA)
- The BMJ: the *British Medical Journal*
- NATURE International Journal of science
- BDJ: The British Dental Journal
For electronic database search, we used free-text and MeSH terms. A sensitive filter was used for identifying RCT studies in PubMed.

In addition, studies were included in the English language only. The references of related articles were cross-checked. However, the last search of the literature was done in May 2018. Besides that, a limited update search was implemented from May 2018 to December 2018.

After identification of all free text keywords and related controlled vocabulary [MeSH] terms for the study concepts of the present systematic review, a researcher combined them with the Boolean operator.

PubMed search strategy (Advance search)

The following electronic search strategy was used to search PubMed databases which were developed according to Cochrane Collaboration for identifying randomized controlled trials (Dickersin et al., 2002):

**Search terms for Nd:YAG Laser:**

#1 Neodymium-Doped Yttrium Aluminum Garnet Lasers

#2 Neodymium Doped Yttrium Aluminum Garnet Lasers

#3 Nd-YAG Lasers

#4 Nd YAG Lasers

#5 Lasers, Nd-YAG

#6 Laser, Nd-YAG
Search terms for Periodontitis:

#12 periodontitis [MeSH]
#13 periodontal disease*
#14 gum disease*
#15 #12 OR #13 OR #14

Search terms for Randomized controlled trials:

#16 randomized controlled trial [pt]
#17 controlled clinical trial [pt]
#18 randomized [tiab]
#19 placebo [tiab]
#20 drug therapy [sh]
#21 randomly [tiab]
#22 trial [tiab]
#23 groups [tiab]
#24 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25 animals [mh] NOT humans [mh]
#26 #24 NOT #25

Search for Nd:YAG Laser AND Periodontitis:
The electronic search strategy above was reviewed and searched by the author and checked from the supervisor. Moreover, the same strategy in CENTRAL (Cochrane Library) was used. Furthermore, an individual utilized Boolean operators, controlled vocabulary (MeSH terms) and the asterisk mark (*) as a truncation in the search strategy.

**Study selection:**

First of all, we will merge search results using reference management software (Mendeley) then we will remove duplicated reports, and we will examine the titles and abstracts to remove obviously unrelated reports. Besides that, we will retrieve the full-text studies of potentially relevant reports. One author will examine the full-text studies for compliance with eligibility criteria. Thus we will identify the eligible studies. In the end, we will make a final decision on study inclusion with the help of the supervisor. Resolving, any disagreements between the two, at any stage of the study selection process, was resolved by discussion.

The study selection was performed with the help of Covidence software (covidence.org).

In details, the study selection process was done in seven steps as follows:

**Step1: Removing duplicates studies**

In this step Covidence played a critical role, it identified and removed all duplicated studies from the literature of candidate studies.
Step2: Apply inclusion/exclusion criteria to titles and abstracts.

One reviewer piloted the inclusion/exclusion criteria in the list of candidate reviews; this was done to ensure that the reviews can be classified correctly. Then the candidate’s reviews were analyzed according to the following inclusion criteria:

1.a. Patients diagnosed with Chronic Periodontitis.

1.b. Randomized controlled studies (RCTs).

1.c. Adult participants (age ≥ year-old).

1.d. Studies that compared SRP with Nd:YAG laser versus SRP alone or placebo.

1.e. Articles in English.

After applying the inclusion criteria in the titles and abstracts of the candidate reviews, we went on exclusion the remains studies.

Step3: Eliminate studies that could meet one or more exclusion criteria.

At this step of the selection process, we emphasized on excluding the studies that meet one or more of the exclusion criteria. Studies are eliminated from the bibliography of candidate studies if the titles and abstracts clearly disqualify them.

2.a. Patients who have a systematic disease that could influence the periodontal tissues.

2.b. Pregnant women.

2.c. People who consume medicine that is known for its effect on periodontal disease or treatment.

2.d. Reports that did not analyze the primary outcomes.

2.e. Periodontal therapy that has done the last six months.

Step 4: Retrieve the full-text of the included studies.

At this stage, we retrieved the full text from the studies that did not excluded and has remained from step two. The screening of full text is vital to make sure that the
accuracy of decision making is to include or exclude studies from the literature of candidate studies. Then, we proceed to step five after retrieving all full-text reports.

**Step 5: Screen the full-text reports of the remaining studies for Inclusion and Exclusion**

In this step, one evaluator screened the full-text reports and applied the inclusion/exclusion criteria to the remaining studies that are included in the literature of candidate studies.

**Step 6: Include studies that meet the Inclusion criteria**

During the screening of the full-text report of the studies, we were trying to ensure that all the studies meet the inclusion criteria and not one or more from the exclusion criteria to include it in our systematic review. In some studies that the methods, results or outcomes are reported incompletely or have some ambiguous, we tried to contact the original study author. When the critical information was not available, a decision to exclude the individual study was justified. Following this stage of the selection process, the reviewer proceeded to exclude studies with reasons further.

**Step 7: Exclude studies with reasons**

In this step, the reviewer excluded studies that had inadequate data or insufficient statistics that could not be pooled into meta-analysis.

In some cases, there were a few study cases that report ambiguous or uncertain results, when that happened, reviewers had to seek more information from the authors before excluding the studies. The systematic reviewers provided descriptions of the reasons why those studies were excluded.

**Step 8: Accept studies for systematic review.**

In the final stage of the selection process, reviewers accept the remaining studies as eligible for systematic review. These studies constitute the sample of studies for analysis and are presumed to be representative of the population of relevant studies. The selection process ends at this point, and coding and analysis of data begin.
**Data collection process:**

To collect data from the eligible studies, we first formed a list of all relevant data items; then the data were managed in Covidence software program. To ensure that all relevant data were captured, one reviewer pilot-tested the data form in one of the included studies. This testing helped in identifying the data that were missing from the form, or likely to be unnecessary. Thus, one reviewer (N.I.) screened each eligible study and extracted the relevant data and enrolled them in Covidence extracted form.

**Data items:**

The data collection form was designed carefully to target the objective of the review and to check the reliability and integrity of the data.

As a consequence, the systematic reviewer extracted the following data from the included studies:

1. Study identification: such as a sponsor, setting, and author's details.
   - Study details:
     - Study ID (First author name, year)
     - Sponsorship source
     - Country, in which country the study occurred
     - Setting, is where the study was located in, ex (hospital, private clinic, school, etc)
     - Any additional comments
   - Author's contact details:
     - Author's name
     - Institution, the name of the institution that the author works in
2. Methods: characteristics of the study.

- Design, the design of the study such as prospective or retrospective cohort study or randomized controlled trials.
- Total study duration, for how long the study took time.

3. Participants characteristics:

- Inclusion criteria, it is the characteristics that the participants must have if they are going to be included in the study. Thus, our inclusion criteria were patients who are diagnosed with chronic periodontitis are older than eighteen years old, and other criteria which detailed in the screening process above.
- Exclusion criteria: which are the characteristics that must not be found in the participants, for example:
  1- Participants with systematic diseases that may influence the periodontal tissues or treatment.
  2- Pregnant women.
  3- Participants who consume any medical known for its effect on the periodontal disease.
- Diagnostic criteria, which means the disease of the participants.
- Baseline characteristics:
  - Age: mean, standard deviation (SD) and range of the age of participants in years
  - A total number of participants in each study and for each intervention group if available.
  - Sex: sex of participants in numbers.

4. Interventions: the total number of intervention groups are three. The first includes using SRP with Nd:YAG laser. The second group relates to the use of SRP alone. And Finally, the third group are using a placebo. The second and third represented the comparators of the intervention. However, we collected the following data for the interventions group:

  - Type of instrument (hand or powered), duration of instrumentation, number of participants and number of teeth tested.
  - Type and parameters of Nd:YAG laser (wavelength, pulse, and watt).

5. Outcome data: there are two groups of outcomes, the primary and the secondary outcomes groups. The primary outcomes such as probing pocket depth, clinical
attachment level, and plaque index are assisted to answer the focused review question. The secondary outcome of interest are bleeding on probing and gingival.

**A. Primary outcomes:**

- Probing pocket depth (PPD): which is the distance between the gingival margin and the pocket depth. The change from baseline to end of the study was measured in millimeters (mm).
- Clinical attachment level (CAL): which is the distance from the cementoenamel junction (CEJ) and the pocket depth measured in millimeters (mm). The change was measured from baseline to end of the study.
- Plaque index (PI): from baseline to end of the study.

**B. Secondary outcome:**

- Modifying in bleeding on probing (BOP) (%) from baseline to end of the study.

We only extract the numeric data whether the data that were presented in text or tables (numerically). Whereas the graphically data were not considered. The extracted data was checked by the reviewer (N.I.)

**Summary measures:**

The outcomes (PPD, CAL, BOP and PI) that mainly extracted from the studies were continuous outcomes. The measurements of these kind of outcomes are the mean value (M), standard deviation (SD) and the number of participants (N). Thus, we were able to extract the following measurements for each outcome:

- Mean value (M) of the outcome in intervention and comparator group.
- Standard deviation (SD) of the outcomes in the two groups.
- Number of each participant (N) who the outcomes were measured in the two groups.
The effect measure we used for the primary and secondary outcomes was the difference in means (MD) and confidence intervals (CI). Mean difference represents the absolute difference in means between the intervention group (SRP + Nd:YAG laser) and the test group (SRP alone) (mean of intervention minus the mean of test group). In other words, mean difference estimates the amount by which the intervention (SRP + Nd:YAG laser) affects the outcome of interest compared with the controlled (SRP alone).

This summary statistic used in computing the meta-analysis because the effect measure are made on the same scale across studies.

Furthermore, when necessary we reconstructed the standard deviation from other statistics, such as 95% confidence intervals and P values.

**Assessment of risk of bias**

To assess risks of bias within included studies we used the Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). Therefore, to facilitate the assessment, the areas covered are sequence generation, allocation concealment, blinding of participants and/or clinical care provider, incomplete data and finally selective outcome reporting and other forms of bias. For each domain in the tool, we will describe the methods for each engaged study, including verbatim quotes. However, we made judgments to the possible risk of bias of the studies and rate them as low, high and unclear risk. The unclear studies will be conducted for further investigation. One author will make these judgments, and any disagreement will be resolved by consulting a supervisor author.

The procedure of risk assessment of bias was worked in Covidance software.

**Statistical analysis**
Meta-analyses were performed for the outcomes of interest by carrying out the following stages: first of all, we calculated the summary effect measures for each individual study. The effect measures for the data in the review are the mean difference (MD) which was calculated from the intervention group mean minus control group mean. To illustrate this point, the best method to interpret the measure effect for continuous data is a mean difference, and because the data in the included studies are continuous, we used it. Second, a weighted average of the intervention effects in each study was estimated. In this way, a pooled intervention effects were produced for each study in the review. This weight may give the study how much it will contribute to the weight average. To obtain the study weight we used the invasive variance (I.V.). The invasive variance measured from the following formula,

\[
\text{Weight} = \frac{1}{\text{Variance of estimate}}
\]

Finally, we utilized a random effect model to estimate the intervention effect through the studies.

We used the random effect analysis model because it offers more value to the results in smaller studies from the fixed-effect model and also it takes account of between study and within study variation, but it gives wider CI from the fixed-effect model.

Furthermore, we conducted the data for meta-analysis by using RevMan5.3. It is a statistical software package (Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Particularly, we computed the mean difference for the outcomes, the weight of each study, the random effect analysis for the nested mean difference, confidence intervals (CI) heterogeneity values and p-values, using RevMan. P-Value less than 0.5 was considered (p < 0.05).
Assessment of heterogeneity, we investigated the clinical heterogeneity of the included studies with respect to study design, interventions, outcomes and the duration of follow-up as the studies seemed to be quite homogenous.

Statistical heterogeneity, to evaluate heterogeneity we first check visually the Confidence intervals (CI) overlap in the forest plots we utilized the chi-squared test (Chi²) (Cochran’s Q) to estimate the heterogeneity. A low p-value less than 0.1 indicate significant heterogeneity. But because this test has a low power we conducted second statistical test. the I² test was used to assess the statistical significance of the heterogeneity. The value of I² test ranges between 0% to 100%, whereas 0% indicates no or minimal heterogeneity and 100% high heterogeneity. Values ≥ 75% indicates considerable heterogeneity.

Two interrelated approached used to investigate the presence of publication bias in meta-analysis. First, we constructed a funnel plot and then we visual detected it. And second we performed regression asymmetry test.

RESULTS

Study selection

A total of 429 publications were found from searching the electronic bibliographic, but none was found from the hand searches. After search of PubMed provided 92 publications, while CENTRAL provided 45 trials and EMBASE/ELSEVIER identified 18 publications. During the first stage, 200 duplicates publications removed, and 229 remained after adjusting for duplication. During the second stage of study selection, the 229 remaining publications screened against title and abstract, of these, 192 publications were discarded because they obviously did not meet the inclusion criteria. The inclusion criteria are the following: patients who were diagnosed with chronic
periodontitis (1.a), randomized controlled studies (RCTs) (1.b.), adult participants (age ≥ year-old) (1.c.), studies that compared SRP with Nd:YAG laser versus SRP alone or placebo (1.d.), and finally, articles written in English (1.e.).

During the third phase, 37 publications assessed for full-text eligibility and were examined in more detail. Particularly, the remained publications have been detected for the excluding criteria. The excluding criteria for the present review were, patients who were diagnosed with chronic periodontitis (2.a.), pregnant women (2.b.), participants who take any medications known for their effects on periodontal disease or periodontal treatment, reports that did not report the outcomes of interest or did not analyze the primary outcomes (2.d.), and finally, periodontal therapy that was done in the last six months (2.e.). Moreover, if the full-text of a report is unavailable, the publication was removed. In Addition, if the sample size of the study was small, which means the number of participants is less than 10 participants, the publication is excluded. However, a second detection of publication was performed in this stage.

As a consequence, 31 publications were discarded because they did not fulfill the inclusion criteria and met at least one of the exclusion criteria. In detail, the publications that did not meet the inclusion criteria are the following: seven publications removed because they have a wrong intervention or comparator, the other two had wrong study design (1.d.), four were not randomized controlled trials (1.b.). Lastly, one study was published in English (1.e.).

The following publications met one or more of the exclusion criteria, three publications did not analyzed the primary outcome and other two did not report the outcome of interest (2.d.). Other studies were finally excluded for different reasons, such as small sample size in one study, or the full article does not exist in three studies, the data was not reported as mean ± SD in two publications, and duplicated reports were find in six publications.

Ultimately, a total of six publications [(Qadri et al., 2010)(Gómez et al., 2011)(Javed et al., 2016)(Slot et al., 2011)(Eltas and Orbak, 2012a)(Eltas and Orbak, 2012b)] fulfilled the required criteria and were included in the present systematic review as well as in the meta-analysis. After checking the references of related papers and systematic reviews, and going through the searching process of studies that have
cited the related papers, we did not come up with any additional studies that can meet the criteria for inclusion.

A flowchart which included informations and different phases throughout the systematic review, that describes the process of study selection is shown in Fig. 1 below.

![Flowchart of study selection process](image)

Fig. 1 Flowchart of study selection process
**Study characteristics**

All six included studies in the review were clinical randomized controlled trials (RCTs), four of them [(Eltas 2012), (Eltas November 2012),(Qadri 2010), (Slot 2011)] used the split-mouth design, while the other two[(Javed 2016),(Gomez 2011)] used prospective RCT, all of them were published in English.

All studies compared the use of Nd:YAG laser therapy as an adjunctive to SRP in the treatment of chronic periodontitis. SRP in all studies was performed by hand and ultrasonic instruments. According to Nd:YAG laser which has been used in the studies, the wavelength of all studies was the same which was 1,064 nanometers, while the other parameters differ, the energy level ranges from 80 to 400 mJ/pulse, a pulse-repetition rate ranges from 10 to 50 Hz, pulse-width varied from 250-350 ms and finally, the time spent in each tooth differs between 60 and 120 seconds.

The duration of follow-up ranges between one and up to 9 months, The (Eltas 2012) study have the longest follow-up duration. Three RCTs [(Eltas November 2012),(Gomez 2011),(Qadri 2010)] reported the changes in PPD and PI in the first month of follow-up, while four studies[(Eltas 2012),(Javed 2016),(Qadri 2010),(Slot 2011)] reported these outcomes at three months. The values of PPD and PI were evaluated in all included studies. Two studies [(Eltas 2012), (Eltas November 2012)] reported CAL gain, whereas the other two [(Javed 2016), (Slot 2011)] reported changes in BOP. However, the outcomes PI and BOP in the study [Gomez 2011] were not pooled into the meta-analysis since different types of indices were utilized.

All patients in the six studies underwent oral hygiene instructions. No side effects, or adverse events related to laser treatment were reported or observed by the patients in the included studies.

Eltas el al. (I)(Eltas 2012) compared the clinical effects of scaling and root planning (SRP) alone with SRP plus Nd:YAG laser in moderate chronic periodontitis. A total of 20 patients underwent the treatment which was performed at about 40 teeth, this treatment was divided into two groups: the test side (n=20) and the control side
(n=20). The tooth in the test side was treated with SRP and Nd:YAG laser, on the other hand, the control side received SRP alone. The outcomes PPD, PI, and CAL values had been recorded at baseline, three and nine months after treatment. The change for PI between the test and control group was similar, no statically significant was observed between the groups at three and nine months after treatment. In contrast, there was a statistically significant difference for PPD and CAL between the test and control groups.

In the study Eltas el al. (II)(Eltas November 2012), they compared the clinical effects of SRP alone with SRP + Nd:YAG laser in smoking and nonsmoking patients with chronic periodontitis (Eltas and Orbak, 2012a). The study was implemented on 208 teeth from 52 participants where 26 of them were smokers, while the other 26 of them were non-smokers. However, the study was performed in four groups: Group 1 included the test teeth in smoking patients and were received SRP+Nd:YAG laser. Group 2 included the control teeth in smoking patients and were treated with SRP alone. Group 3 included the test teeth, in non-smoking patients, who received treatment including SRP + Nd:YAG laser. And finally, Group 4 which included the control teeth in non-smokers were treated with SRP alone. Each group contains of 52 teeth (n = 52) . Concerning clinical parameters, PD, CAL PI and GI were measured at baseline, at one and six months after treatment. The mean change for the parameters PD, GI and PI for all groups were statically significant the difference at one and six months (p<0.05), while the change for all groups in CAL was statically significant(p>0.05), at one and at six months after treatments. Besides, the changes in non-smokers group were higher from that in smokers group despite that no statically significant detected between the two groups. There was no significant difference in SRP application versus SRP + Nd:YAG laser for all of the clinical parameters (p>0.05)(Eltas and Orbak, 2012a).

Whereas, Gomez et al. ( III)(Gómez 2011) compared the use of SRP alone versus SRP with Nd:YAG laser in the treatment of chronic periodontitis. Thirty patients with moderate to advanced chronic periodontitis were randomly assigned in the study.
Measurements for baseline, one and two months of PPD, BOP, and PI were recorded.

The differences for PPD, PI, and BOP were statistically significant in both groups (SRP and SRP + Nd:YAG), comparing the data at baseline, and one and two months after treatments \((p<0.05)\) (Gómez et al., 2011).

Javed et al. (IV) (Javed et al., 2016) compared the effect of SRP and Nd:YAG therapy in patients with moderate periodontal disease (PD), as well as in patients with and without coronary artery disease (CAD). The study conducted 87 patients, who were divided into two groups. Group 1, CAD and PD with 44 patients. Group 2, PD alone with 43 patients. The patients in each group were randomly divided into two subgroups: (a) SRP alone and (b) SRP + Nd:YAG laser therapy. The periodontal parameters PPD, PI and BOP, were registered at baseline and three months post-therapy. Regarding the second group (PD alone), at three months of follow-up, PPD, PI and BOP were significantly higher in patients treated with SRP alone compared to those treated with SRP + Nd:YAG laser therapy.

Qadri et al. (V) (Qadri, 2010) compared the clinical effects of Nd:YAG laser and SRP with SRP alone. A total of thirty participants underwent two treatments modalities. The teeth on the control side (204 teeth) were treated with SRP alone, whereas on the test side (201 teeth), were received SRP and laser therapy. The PPD, PI, GI, and GCF were measured at one week and three months after treatment. At three months of follow-up, significant improvement was detected in all clinical parameters at the test sides compared to the control sides (Qadri et al., 2010).

Slot et al. (VI) (Slot, 2011) tested whether the use of Nd:YAG laser as an adjunctive to SRP will lead to better clinical improvement than SRP alone. However, clinical measurements for the parameters PPD, BOP, and PI were performed at baseline and after three months of the treatment. Nineteen patients with moderate to severe periodontitis were enrolled in the study and treated with SRP, additional treatment
with laser was provided in the test side. At three months after treatment, improvement in all clinical parameters was reported, compared with baseline in the two treatments modalities, but no statistically significant differences were found for all the parameters between SRP group and SRP + laser treatment, at baseline and the end of the study (Slot et al., 2011).

**Assessment of risk of bias**

The results from assessment risk of bias within studies presented in Table 1 below,

<table>
<thead>
<tr>
<th>Study ID</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>Total estimated risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eltas 2012</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Eltas, November 12</td>
<td>L</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Gomez 2010</td>
<td>U</td>
<td>L</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Javed 2016</td>
<td>L</td>
<td>U</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Qadri 2010</td>
<td>L</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Slot 2011</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

Table: *where U=Unclear, H=high and L=Low*
We used the Cochrane risk of bias tools, which includes six domain as illustrated as follows:

1. Sequence generation (Selection bias) “A”
2. Allocation sequence concealment (selection bias) “B”
3. Blinding of participants and personnel (Performance bias) “C”
4. Blinding of outcome assessment (Detection bias) “D”
5. Incomplete outcome data (Attrition bias) “E”
6. Selective outcome reporting (Reporting bias) “F”

After the results were determined for each study, an overall estimate of the risk of bias” Low, moderate, or high) was made for each one of the studies. If all of the selected criteria were met, then a low risk of bias was estimated. If one or more of the criteria partly met, then it is a moderate risk, and finally, if one or more of the criteria were not met, then it is estimated for a high risk of bias.

**Meta-analysis**

Data for the outcomes PPD and PI were available for all studies, randomizing and reporting data for 168 patients. Data for the outcomes PI and BPO in one study [Gomez 2011] were not possible to pool in the meta-analysis because they have different type of summary measures. According to Qadri study [Qadri 2010], the data of a one week of follow-up were counted in the analysis of a one-month follow-up. For study [Eltas November 2012] we incorporated the data from the non-smoking group in the meta-analysis. The same for [Javed 2016], we used the data from the group PD alone. Another point worth mentioning is that that the data from the study [Javed 2016] were converted to the standard deviation( SD) in order to fit in the meta-analysis because the values were presented as means ± 95% CI.

The results from meta-analysis for the outcome PPD are reported in Fig. 1. The data for PPD at 1 month was extracted from three studies [Eltas November...
2012). (Gomez 2011), (Qadri 2010)]], while at 3 months they was extracted from four studies [(Eltas 2012), (Javed 2016), (Qadri 2010), (Slot 2011)].

At 1 month no significant differences were detected in reduction of PPD between SRP and SRP + Nd:YAG (MD = 0.03, 95% CI range: −0.54 to 0.61, \( p = 0.91 \)), but high heterogeneity was detected between studies (\( \chi^2 = 26.46, \ p < 0.00001, I^2 = 92\% \)) as shown in the upper diamond in fig. 1. At 3 months, no statistically significant difference was observed as MD = −0.61 (95% CI range: −1.42 to 0.20, \( p = 0.14 \)) and high heterogeneity was detected (\( \chi^2 = 120.86, \ p < 0.00001, I^2 = 98\% \)).

At 1 month, data for PI were extracted from just two studies [(Eltas November 2012) and (Qadri 2010)] and four studies [(Slot 2011), (Qadri 2010), (Javed 2016), (Eltas 2012)] at 3 months. At 1 month, no statistically significant difference were observed between SRP and SRP+Nd:YAG (MD = −0.03, 95% CI range: −0.45 to 0.38, \( p = 0.88 \)), and with no evidence of heterogeneity (\( \chi^2 = 0.89, \ p = 0.34, I^2 = 0\% \)). The results at 3 months showed no significant differences between the two groups as MD = -0.56 (95% CI range: −1.53 to 0.41, \( p = 0.26 \)) and with high heterogeneity (\( \chi^2 = 224.85, \ p < 0.00001, I^2 = 99\% \)) (Fig 2).
The data for BOP were extracted from two studies [(Javed 2016), (Slot 2011)] at 3 months of follow-up. No statistically significant difference was observed between the control and the test groups (MD = -1.04, 95% CI range: -3.39 to 1.31, p = 0.39), and high heterogeneity was detected (χ² = 412.00, p < 0.00001, I² = 100%) the results are represented in Figure 3.

Apart from this, no meta-analysis was performed for the outcome CAL gain.

Considering the small number of the included RCTs (<10) the metaregression test and subgroup analysis were not performed.

The funnel plots for PPD PI and BOP were worked and extracted from Revman, as it shown in the figures below.
For PPD

FOR PI

For BOP
DISCUSSION

The present systematic review and meta-analysis were undertaken for the scoop to assess the effectiveness of Nd:YAG laser as an adjunctive to scaling and root planning in the treatment of chronic periodontitis. As a consequence six publications with a total of 168 participants were entered to the analysis to explore the changes in the clinical parameters in patients treated with Nd:YAG laser, these clinical parameters are a reduction in PPD, changes in PI, reduction in BOP and CAL gain.

Moreover, meta-analysis were conducted for three parameters (PPD, PI and BPO), we did not perform meta-analysis for CAL gain because first it was presented in just two studies and second these two studies have different follow-up durations. However, improvement in the three parameters was observed in the intervention group (Nd:YAG laser) but it was not statically significant.

Improvement in PPD at the first month of follow-up was observed in the intervention group (Nd:YAG laser) in constrasting of the control group. For one study (Gómez et al., 2011) the reduction in PPD was not significant in contrary of the other two studies (Eltas, November, 2012 and Qadri 2010) (Eltas and Orbak, 2012a) which reported a significant higher PPD reduction from the adjunctive use of Nd:YAG laser. At 3 months of follow-up this reduction were observed in three studies [(Eltas 2012), (Javed 2016) and (Qadri 2010)] between the two groups, but did not observed in one study (Slot 2011). However, PI reduction at one month of follow-up significantly obersed in favour of SRP and Nd: YAG group in one study (Qadri 2010), whereas no PI reduction between the two groups were detected in the other study (Eltas, November, 2012). At three months of follow-up four included studies [(Qadri 2010), (Eltas 2012), (Javed 2016) and (Slot 2016)]

Lastly, a significant reduction in BOP was detected in favour of SRP + laser in one report (Javed 2016) whereas in the other report it was not significant (Slot 2011) at the three months of follow-up, as it illustrated in the forest plots above.
CONCLUSIONS

It concludes that no evidence was detected, the results for this systematic review and meta-analysis found no evidence of the effectiveness of Nd:YAG laser utilized as an adjunctive compared to SRP alone in the treatment of chronic periodontitis.

The systematic review was performed according to Cochrane Collaboration recommendations.

SUGGESTION FOR FURTHER WORK

In the near future, it is advised to perform well-designed RCTs to clear out the effectiveness of SRP with Nd:YAG laser in contrast to SRP alone.

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