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Review

Adjunctive antimicrobial photodynamic therapy to conventional chemo-mechanical debridement of infected root canal systems: A systematic review and meta-analysis

Maryam Pourhajibagher[a], Abbas bahador[b,*]

[a] Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[b] Oral Microbiology Laboratory, Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: To investigate the efficacy of antimicrobial photodynamic therapy (aPDT) adjunctive to conventional chemo-mechanical debridement of root canal system in patients with endodontic infections.
Methods: A meta-analysis was done according to the Cochrane Collaboration recommendations and PRISMA statement. Two independent reviewers performed an extensive literature search on electronic databases of MEDLINE, EMBASE, and SCOPUS up to January 2019. The search strategy was done from the following terms: antimicrobial photodynamic therapy OR photo-activated disinfection AND root canal therapy OR endodontic therapy OR root canal infection OR endodontic infection. The I^2 test was used for determine the inter-study heterogeneity. Publication bias assessment carried out on the studies using the Egger's regression test.
Results: Sensitivity analysis of 10 randomized clinical trials (RCTs) revealed differences in microbial load reduction (0.143, 95% CI [0.06, 0.30], P = 0.000) in favor of aPDT plus conventional chemo-mechanical debridement. A high degree of heterogeneity (P = 0.000; Q- value = 154.74; I^2 = 94.18%) was noticed among photosensitizer and light parameters. Subgroup analysis demonstrated the absence of heterogeneity in RCTs, with low risk of bias for microbial load reduction gain. No evidence of publication bias was determined.
Conclusions: Although the aPDT parameters may vary from one RCT to the next, all studies found a reduction in microbial load with adjunctive use of aPDT; however, further high-quality RCTs focused on the standardized aPDT parameters are needed.

1. Introduction

The main objective of endodontic treatment is the elimination and possible eradication of the involved microbiome, their byproducts and virulence features from the root canal system, to reduce or arrest the progression of apical periodontitis by shaping, cleaning and disinfecting an infected root canal space [1]. Standard treatment of endodontic infections, which mainly consists of mechanical instrumentation and irrigation with disinfecting solutions, chemo-mechanical procedure, usually results in significant clinical improvement [2]. However, chemo-mechanical procedures may fail to clean and asepsis remote areas of the root canal system [3,4]. Therefore, adjunctive modalities to chemo-mechanical procedures in endodontic therapy, such as root canal medicaments, particularly antibiotics, and antimicrobial photodynamic therapy (aPDT) have been evaluated [5,6]. However, inter-appointment intracanal medication could be potentially accompanied by side effects including tooth discoloration and the development of resistant bacterial strains [7]. It has not been reported evidence of resistance development in the target microorganisms after only once and repeated applications of aPDT [8].

From the point of view of photosensitizer, photoactivatable substance, and microorganism interaction, the application of aPDT is based on the following principle. The photosensitizer is able to be taken up preferentially by microorganisms. Following activation of photosensitizer by corresponding light wavelength in the presence of oxygen, it generates free radicals and singlet oxygen species in the site to be treated causes an oxidative stress response and eventual microbial death [7,8]. Many endodontic microbiome are susceptible to irradiation in the presence of photosensitizers, including methylene blue (MB), toluidine blue O (TBO), and indocyanine green (ICG). These findings suggest that aPDT could be potentially advantageous in endodontic therapy [9].

* Corresponding author at: Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Keshavarz Blvd, 100 Poursina Ave., 14167-53955 Tehran, Iran.

E-mail addresses: abahador@sina.tums.ac.ir, ab.bahador@gmail.com (A. bahador).

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An earlier study [10] reviewed 9 articles on this topic, but more than 100 new original articles have been published since then. Very few experimental studies were included in a subsequent review without any analysis [10]. Since a variety of natural and synthetic photosensitizer and corresponding light wavelength has been employed during aPDT in endodontic therapy, divergent and controversial results are reported. Even when the same photosensitizer and corresponding light wavelength were used, the variation of photosensitizer concentration, pre-irradiation time, irradiation time and light powers i.e. diversity of treatment protocols, require a lot of accuracy to interpret the results [11]. According to a more recent systematic review [8] which focused only on photosensitizers, light sources, and aPDT mechanism of action, limitations and clinical procedures without any appraisal, there is limited information and sometimes conflicting data pertaining to the use of aPDT in endodontic treatment. A number of studies have revealed a potential role for aPDT in endodontic therapy [7,9,12–23]. Whereas those carried out on root canal biofilms grown *in vitro* have delivered promising results, the data from *in vivo* clinical trial studies are less clear [7].

To date, there had been no previous systematic reviews analytically addressing the question of whether aPDT plus chemo-mechanical lead to more favorable root canal disinfection over conventional chemo-mechanical alone. Therefore, the purpose of current study is to systematically review and critically analyze the effectiveness of aPDT plus conventional chemo-mechanical disinfection i.e. reduction of the microbial load in primary endodontic infections when compared with conventional chemo-mechanical alone. The tested null hypothesis (H0) was that there would be no significant difference in reducing the root canal microbial load when using the aPDT plus conventional chemo-mechanical contemporary vs. the conventional chemo-mechanical alone.

2. Methodology

2.1. Focused question

According the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [11], a question was constructed that the addressed focused question was: “Can aPDT plus chemo-mechanical lead to more favorable root canal disinfection over conventional chemo-mechanical alone?”

2.2. Search strategy for identification and selection of the studies

This study was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews at http://www.crd.york.ac.uk/PROSPERO, registration number ID106071).

2.3. Study selection and data collection

The individual search algorithms, developed for MEDLINE, EMBASE, and SCOPUS databases from January 2006 to January 2019 for relevant studies. The selection process is described in Fig. 1. Electronic database searches were done using various combinations of text words: antimicrobial photodynamic therapy OR photo-activated disinfection AND root canal therapy OR endodontic therapy OR root canal infection OR endodontic infection.

2.4. Eligibility criteria

Articles were included according to PICOS:

Population (P): Subjects of both primary and secondary endodontic infections

Intervention (I): Treatment of endodontic infections with aPDT

Comparison (C): Before and after of aPDT

Outcome (O): Microbial load i.e. count of microorganisms

Study (S): Clinical studies

The following eligibility criteria were entailed: RCT; *in vivo* studies; studies reporting microbial load before and after aPDT application and; studies published in English language only. Duplicate articles, literature reviews, letters to the editor, short commentaries, case reports, *in vitro* studies, *ex vivo* studies, dissertations, studies with animals, congress abstracts, and studies reported in languages other than English were excluded.

2.5. Data synthesis

Quality assessment of titles and abstracts of included articles was conducted independently by two authors (Bahador and Pourhajibagher). The information from the accepted studies was tabulated. As well as, the aPDT parameters were evaluated by type of photosensitizer, photosensitizer concentration, light source, laser wavelength (nm), energy (J), energy fluence (J/cm^2), output power (mW), power density (mW/cm^2), and duration of irradiation.

2.6. Statistical analysis

Meta-analysis was conducted for microbial load i.e. bacterial colony forming unit (CFU)/mL. The mean differences between the test and control groups were estimated as the effect size measures. Data analysis was performed using Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Englewood, NJ, USA). The heterogeneity comparison was checked by Cochrane Q-statistic test and I^2 test. Random effects models were used to estimate the average prevalence because of its conservative summary estimate and because in all calculations, I^2 was above 50%. Fixed-effects model was used when heterogeneity was not statistically significant ($P > 0.05$).

3. Results

3.1. Characteristics of included studies

A flow diagram of the search strategy is presented in Fig. 1 according to PRISMA. The electronic search process yielded a total of 663 potentially eligible records, of which 274 entries were removed after deduplication. After screening of the titles and abstracts, 373 articles were excluded. A total of 16 papers were selected for full-text reading. Of these 16 studies, 4 studies were further excluded. After the final stage of selection, 12 studies were included in the systematic review for qualitative analysis (Table 1).

3.2. Quality assessment of risk of bias

Fig. 2 demonstrates the evaluation of the inner methodological risk of bias, as advised in section 16.1.2 of the Cochrane Handbook for assessing risk of bias. In general, the results were well described in all selected papers and no study had attrition bias due to missing data. All the included RCTs were randomized controlled trials except for 3 studies [13,16,17]. As a result, the risk of bias in this systematic review and meta-analysis study was more frequent in randomization. Quality assessment of all the 12 studies was regarded as high with the score of 7 and 8 (Table 2).

3.3. Microbiological outcomes

In most studies, microbial load was used as a gold standard method for detecting the antimicrobial effect of aPDT. The type of investigated microorganisms has been reported in Garcez et al., 2010, Jurič et al., 2014, Ahangari et al., 2017, Miranda et al., 2017, Pourhajibagher et al., 2018, and da Silva et al., 2018 studies. The mean reduction in the microbial diversity and microbial load of the infected root canal after

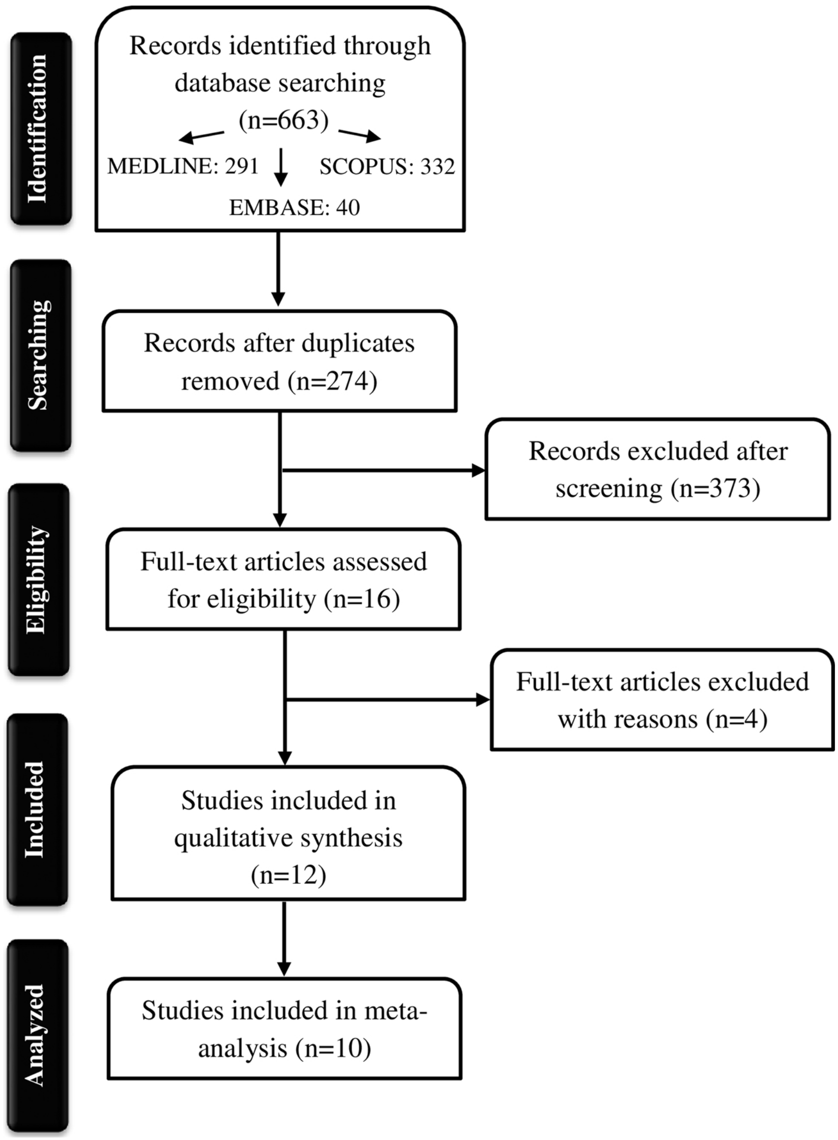


Fig. 1. PRISMA flow diagram for studies retrieved through the searching and selection process.

aPDT was significant. As the studies show, there was a significant difference in reduction of microbial load in aPDT group with the conventional treatment groups.

3.4. Photosensitizer parameter of the included studies

The photosensitizers used included toluidine blue (TBO), methylene blue (MB), indium gallium aluminum phosphorus (InGaAlP), polyethylenimine chlorin (e6), and phenothiazinium chloride, (Table 3). Mota et al., [15], Garcez et al., [16], Asnaashari et al., [17], Miranda et al., [19], Ahangari et al., [20], Rabello et al., [21], and da Silva et al. [23], used MB as the photosensitizer in their studies. TBO was used as a photosensitizer in studies by Bonsor et al., [12], Asnaashari et al. [18], and Pourhajibagher et al., [22], whereas Garcez et al. [13], and Jurič et al. [14], evaluated polyethylenimine chlorin (e6) and phenothiazinium chloride, respectively. Different concentrations of photosensitizers were reported in the most of the studies.

3.5. Laser parameter of the included studies

The data collected from the 12 selected studies regarding the laser parameters are summarized in Table 3. Most of the studies [12,13,16,17,19–22] used diode laser. The wavelengths of the lasers used in the included studies [13,16,17,19–22] ranged between 635 nm and 810 nm. In the other studies, Helbo laser [14], XT-EC laser [15], Fotosan LED [18], and InGaAlP laser [23] with the wavelength ranges between 635 nm and 660 nm were used. The optic fibre diameter ranged from 200 to 1000 mm and the output power ranged between 40 and 220 mW. Asnaashari et al. [18], did not describe the output power. The duration of irradiation ranged between 10 and 360 s. Energy fluence was reported in three studies [15,18,21] and power density was determined in two studies [15,18]

3.6. Meta-analysis

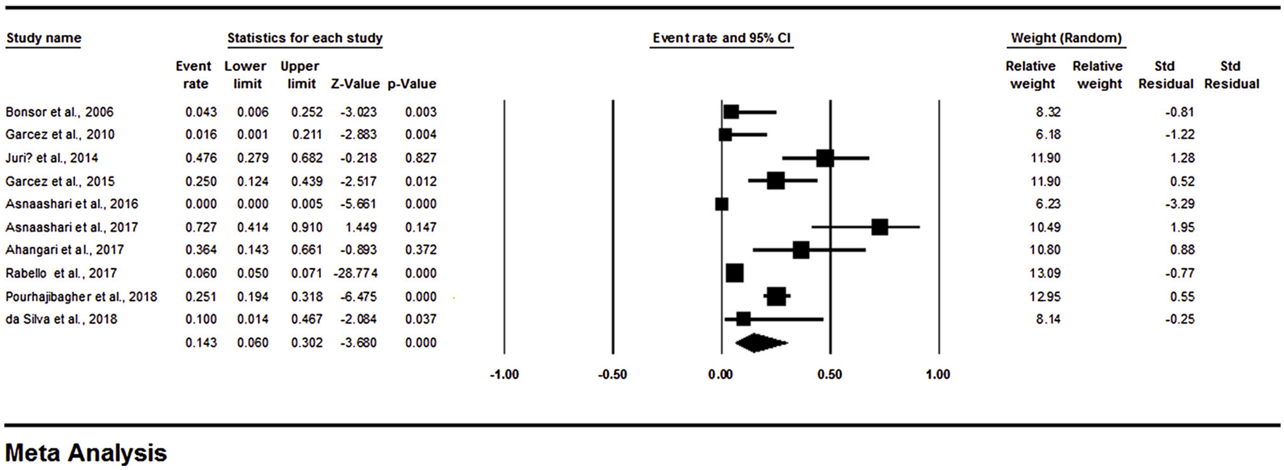
Two articles [15,19] were not included in the meta-analysis due to missing data. After checking the heterogeneity comparison, random effects models were used (Q- value = 154.74; I^2 = 94.18%). The Forest plots (Fig. 2) demonstrated that all of the meta-analysis data presented a significant difference before and after of aPDT. For the total microbial load, i.e. viable microorganisms count analyses, mean difference and 95% confidence interval was 0.143 [0.06, 0.30]; (P = 0.000). As shown in Fig. 3, based on the Funnel plot of meta-analysis, some evidence for publication bias was observed. According to the results, the estimated

Table 1
General characteristics of included studies.

Author/Year	Sample size	Age	Study groups	Main outcomes
Bonsor et al., 2006 [12]	64	16 to 70 years	Group 1: aPDT Group 2: 20% citric acid and 2.25% NaOCl solutions + aPDT	The number of culturable bacteria was lower in group 1 compared with group 2. aPDT showed best results when compared to conventional irrigant solution.
Garcez et al., 2010 [13]	30	17 to 52 years	Group 1: Conventional endodontic therapy Group 2: aPDT Group 3: Conventional endodontic therapy + aPDT	The use of aPDT added to conventional endodontic treatment leads to a further major reduction of microbial load.
Jurič et al., 2014 [14]	21	20 to 45 years	Group 1: Endodontic treatment with 2.5% NaOCl and 17% EDTA Group 2: aPDT Group 3: Conventional endodontic therapy + aPDT	The combination of endodontic treatment and aPDT was statistically more effective than endodontic treatment alone.
Mota et al., 2015 [15]	30	3 to 6 years	Group 1: Conventional treatment with 2.5% NaOCl Group 2: aPDT	aPDT can assist in the achievement of successful endodontic treatment in primary teeth.
Garcez et al., 2015 [16]	28	17 to 52 years	Group 1: Conventional treatment using ultrasonic retrotip Group 2: Conventional treatment using ultrasonic retrotip + aPDT	The microbiological samples showed an overall significant reduction (5 log) with aPDT. aPDT highly improves the microbial reduction compared to the traditional technique
Asnaashari et al., 2016 [17]	20	NR	Group 1: aPDT Group: Diode laser only	CFU/mL amounts showed statistically significant reduction in both groups
Asnaashari et al., 2017 [18]	20	NR	Group 1: aPDT Group 2: Ca(OH)2 therapy	The number of CFU/mL was lower in group 1 compared with group 2.
Miranda et al., 2017 [19]	32	6 months to 2 years	Group 1: CMD Group 2: aPDT	Group 2 presented similar CFU/mL reduction compared with group 1.
Ahangari et al., 2017 [20]	20	NR	Group 1: aPDT Group 2: Ca(OH)2 therapy	Group 1 presented similar CFU/mL reduction compared with group 2.
Rabello et al., 2017 [21]	24	Mean age 43 years	Group 1: CMP using the single-file reciprocating technique +2.5% NaOCL and 17% EDTA + aPDT Group 2: Ca(OH)2 + SSL	The group 1 was effective in reducing bacterial load more than group 2.
Pourhajibagher et al., 2018 [22]	36	19 to 58 years	Group 1: aPDT Group 2*: Conventional treatment	There was a significant decrease in the microbial diversity and count of the infected root canal after aPDT.
da Silva et al., 2018 [23]	10	17 to 65 years	Group 1: CMI Group 2: aPDT	aPDT may be an effective adjunct therapy, resulting in a reduction of bacteria.

Note: Abbreviations: aPDT: Antimicrobial photodynamic therapy, NR: Not reported, CFU: Colony forming unit, NaOCl: Sodium hypochlorite, EDTA: ethylenediaminetetraacetic acid, Ca(OH)2: Calcium hydroxide, CMD: Chemo-mechanical debridement, CMP: Chemo-mechanical preparation, SSL: Saline solution, CMI: Chemical-mechanical instrumentation.

* Included as a clinical trial study after the contact with the corresponding author.



Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
Bonsor et al., 2006	0.043	0.006	0.252	-3.023	0.003	8.32	-0.81
Garcez et al., 2010	0.016	0.001	0.211	-2.883	0.004	6.18	-1.22
Juri? et al., 2014	0.476	0.279	0.682	-0.218	0.827	11.90	1.28
Garcez et al., 2015	0.250	0.124	0.439	-2.517	0.012	11.90	0.52
Asnaashari et al., 2016	0.000	0.000	0.005	-5.661	0.000	6.23	-3.29
Asnaashari et al., 2017	0.727	0.414	0.910	1.449	0.147	10.49	1.95
Ahangari et al., 2017	0.364	0.143	0.661	-0.893	0.372	10.80	0.88
Rabello et al., 2017	0.060	0.050	0.071	-28.774	0.000	13.09	-0.77
Pourhajibagher et al., 2018	0.251	0.194	0.318	-6.475	0.000	12.95	0.55
da Silva et al., 2018	0.100	0.014	0.467	-2.084	0.037	8.14	-0.25
	0.143	0.060	0.302	-3.680	0.000		

Fig. 2. Forest plots of the meta-analysis of aPDT to treatment of endodontic infections.

ranks of correlation coefficients of Begg and Mazumdar rank and Egger´s regression intercept were 0.08 and 0.19, respectively.

3.7. Main outcome of the studies

All studies included reporting clinical endodontic therapy, showed that aPDT was effective in the elimination of microorganisms from infected root canals. When compared with conventional theatment, none of the studies showed the superiority of conventional therapies compared with aPDT.

4. Discussion

Most of the available information on antimicrobial, anti-biofilm and anti-virulent properties of aPDT still originates from *in vitro* studies, which are frequently cited to support the use of this technique [24]. The efficacy of aPDT for the *in vivo* treatment of endodontic infections as an independent treatment or as an adjunct to conventional chemo-mechanical procedure, were investigated in few studies with small sample sizes. Despite the heterogeneity found among the studies, based on meta-analysis results from 10 *in vivo* included in this review, aPDT as an adjunct to chemo-mechanical procedure statistically significant reduced microbial load of infected root canal system. This may, at least in part, suggest that aPDT may be an adjunct therapy in patients with infected root canal, where this is related to an effect on bacteria that invade periapical tissue. Moreover, aPDT has neither been shown lead to the development of resistant bacterial species, nor does it to be safe with no mutagenic effects or toxic [25,26]. In this meta-analysis, two studies [20,23] reported no statistically significant gains in microbial load reductions that favored combined therapy (aPDT plus chemo-mechanical versus chemo-mechanical alone). Interestingly, subgroup analysis revealed that studies adopting MB as photosensitizer indicated that the adjunctive use of aPDT to chemo-mechanical procedure could provide additional benefits, when compared with chemo-mechanical procedure alone, in terms of microbial load reductions. However, it should be noted that two RCT studies [17,20], may have incorrectly accepted the null hypothesis (no statistically significant gains in microbial load reductions) because using of an incorrect irradiation wavelength (810 nm) for activation of MB as photosensitizer and a low time of application (10 and 40 s/site). Unfortunately, no other subgroup analysis could be done to assess the influence of the aPDT parameter including irradiation time and the photosensitizers (type and concentration) on microbial load, due to evidence of heterogeneity between the studies. This heterogeneity is explained by the lack of standardization of aPDT protocols and the variation in study designs. In the 12 RCTs that included the current study, for example, six different photosensitizers and corresponding wavelength with variety of power density were used, which may, of course, lead to different results and conclusions. However, studies with similar design and standardized aPDT protocols are still necessary to assess this additional benefit of aPDT. In the present study, only one included study investigated the effect of aPDT on the variety of endodontic microorganisms [22]. It was revealed aPDT as an adjunct to chemo-mechanical procedure statistically significant reduced microbial variety of infected root canal system. Considering that the progression of periapical lesion in root canal infection is related to certain highly pathogenic bacteria [27], it would seem important that future RCTs also evaluate such parameters that are closely related to the progression and response of the endodontic infections to treatment.

4.1. Quality of the evidence

The Consolidated Standards of Reporting Trials (CONSORT) [28]-based quality analysis revealed that all studies were at low risk of bias, then, the quality of the included studies did not seem to affect the results of the meta-analysis. The current meta-analysis used a wide search strategy with no language restrictions and included rigorous inclusion/exclusion criteria. Although the inspection of the funnel plot for microbial load reductions (Fig. 3) demonstrated the presence of asymmetry, the Egger´s regression test showed that these differences were not significant. Hence, it may be assumed that the possibility of publication bias may not be relevant. The results of the trials included can be valid, since all of 10 studies met all the CONSORT recommendations for quality assessment of RCTs. The criteria for randomization of patients, for example, was not clear and was considered unsuitable in three of the 12 included studies [13,16,17]. Study model RCT as the most reliable form of scientific evidence has the potential advantages including providing high statistical power even when the number of patients is small and reducing error variance of experiments. However, this model has disadvantages such as costs, and conflict of interest dangers [28]. Another aspect that must be noted is that although conventional chemo-mechanical therapy (alone) is predictable in endodontic infections, in all studies where it was used as a control, following aPDT there was a significant improvement in reduction of microbial load relative to measurements taken at baseline [12–23]. Finally, this systematic review and meta-analysis has refused the null hypothesis (no statistically significant difference between the compared aPDT plus chemo-mechanical versus chemo mechanical alone in reduction of microbial load in the treated infected root canal system and has accepted our hypothesis is that the adjunctive effect of aPDT to conventional chemo-mechanical when compared with conventional chemo-mechanical alone in disinfection of root canal space.

Table 2
Quality assessment of the selected studies (The Cochrane Collaboration tool for assessing risk of bias).

Author/Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assesment	Incomplete outcome data	Selective reporting	Inclusion and exclusion criteria	Sample size calculation	Score	Estimated risk of bias
Bonsor et al., 2006 [12]	+	+	+	+	+	+	+	+	8	Low
Garcez et al., 2010 [13]	–	+	+	+	+	+	+	+	7	Low
Jurič et al., 2014 [14]	+	+	+	+	+	+	+	+	8	Low
Mota et al., 2015 [15]	+	+	+	+	+	+	+	+	8	Low
Garcez et al., 2015 [16]	–	+	+	+	+	+	+	+	7	Low
Asnaashari et al., 2016 [17]	–	+	+	+	+	+	+	+	7	Low
Asnaashari et al., 2017 [18]	+	+	+	+	+	+	+	+	8	Low
Miranda et al., 2017 [19]	+	+	+	+	+	+	+	+	8	Low
Ahangari et al., 2017 [20]	+	+	+	+	+	+	+	+	8	Low
Rabello et al., 2017 [21]	+	+	+	+	+	+	+	+	8	Low
Pourhajibagher et al., 2018 [22]	+	+	+	+	+	+	+	+	8	Low
da Silva et al., 2018 [23]	+	+	+	+	+	+	+	+	8	Low

Table 3
Laser and photosensitizer parameters of included studies.

Author/Year	PS/concentration	Light source	Fiber (μm)	Wavelength (nm)	Energy (J)	Energy fluence (J/cm^2)	Power (mW)	Power density (mW/cm^2)	Irradiation time
Bonsor et al., 2006 [12]	TBO / NR	Diode laser	NR	633 ± 2	12	NR	100	NR	120 s
Garcez et al., 2010 [13]	polyethylenimine chlorin (e6) / NR	Diode laser	200	660	9.6	NR	40	NR	240 s
Jurič et al., 2014 [14]	Phenothiazinium Chloride / 10 mg/ml	Helbo laser	450	660	6	NR	100	NR	60 s
Mota et al., 2015 [15]	Chimiolux® MB / 0.005%	XT-EC laser	600	660	4	43	100	108	40 s
Garcez et al., 2015 [16]	MB / 60 μM	Diode laser	200	660	15	NR	40	NR	360 s
Asnaashari et al., 2016 [17]	MB / 0.01%	Diode laser	200	810	NR	NR	200	NR	40 s
Asnaashari et al., 2017 [18]	TBO / 0.1 mg/mL	Fotosan LED	1000	635	NR	0.0012–0.0044	NR	2–4	60 s
Miranda et al., 2017 [19]	MB / 25 μg/mL	Diode laser	300	660	NR	NR	100	NR	300 s
Ahangari et al., 2017 [20]	MB / 50 μg/mL	Diode laser	200	810	NR	NR	200	NR	10 s
Rabello et al., 2017 [21]	MB / 0.1 mg/mL	Diode laser	300	660	NR	129	60	NR	120 s
Pourhajibagher et al., 2018 [22]	TBO / 100 μg/mL	Diode laser	250	635	NR	NR	220	NR	60 s
da Silva et al., 2018 [23]	MB / 100 μg/mL	InGaAlP laser	NR	660	NR	NR	100	NR	40 s

Note: Abbreviations: PS: Photosensitizer, MB: Methylene blue, TBO: Toluidine blue O, aPDT: Antimicrobial photodynamic therapy, NR: Not reported, CFU: Colony forming unit, LED: Light emitting diode, InGaAlP: Indium gallium aluminum phosphorus.

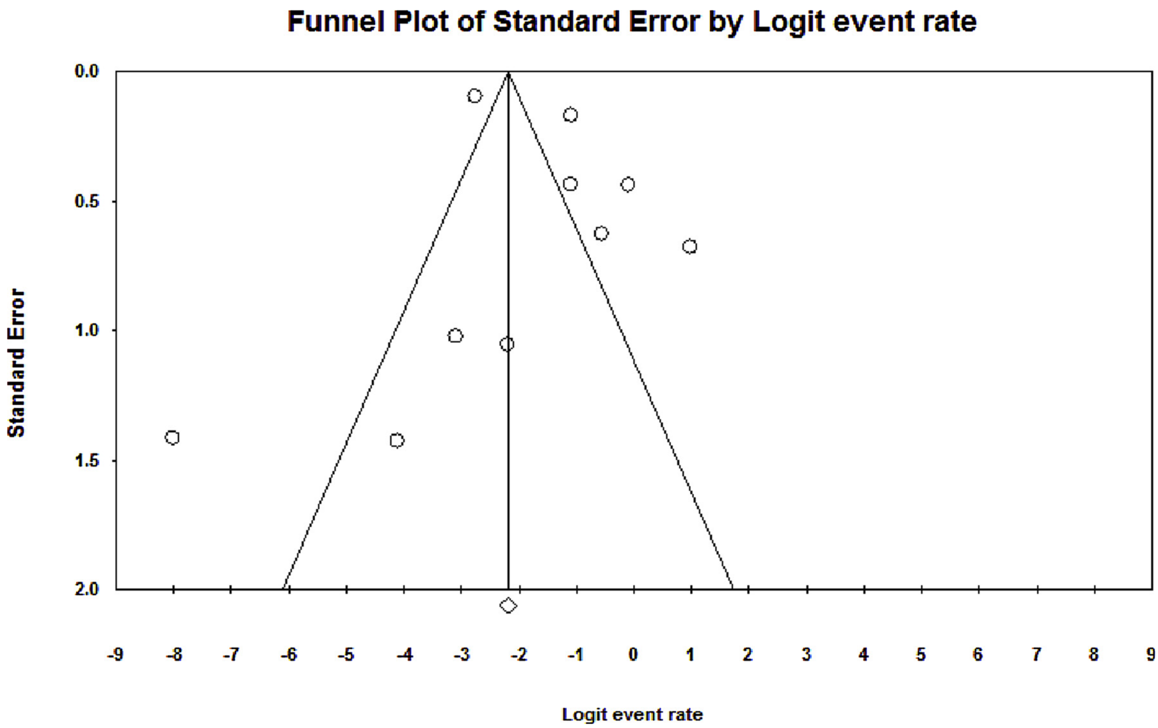


Fig. 3. Funnel plots of the meta-analysis to investigate publication bias.

4.2. Agreements and disagreements with other studies or reviews

According to the best of our knowledge, no other systematic review evaluated the effects of aPDT as a primary mode of treatment or as an adjunct to chemo-mechanical procedure on the case of microbial load (CFU or log_{10}) reduction in root canal system in patients with endodontic infections. However, three systematic reviews [7,10,24] summarize recent developments of aPDT in the field of dentistry and endodontic regarding its mechanism of action, light sources, photosensitizers, limitations, clinical applications and side effects to address the question: Does aPDT improve root canal disinfection? Gursoy et al. [10] concluded that aPDT seems to be a promising adjunctive supplement, specifically in persistent/ secondary cases where *Enterococcus faecalis* plays a main role. However, further clinical trials are required to make more reliable their conclusions regarding the use of aPDT in root canal treatment. Diogo et al. [24] based primarily on available *in vivo* studies concluded that the efficacy of aPDT as an antimicrobial adjuvant remains promising with an additional potential benefit in root canal disinfection where highly resistant bacteria are present in the root canal system. According to Plotino et al, [7] aPDT as an adjunctive modality after conventional chemo-mechanical debridement of root canals is a minimally invasive approach for further reduction in microorganisms that remain viable in the root canal system. Further trials are necessary to determine the appropriate aPDT parameters including design of different photosensitizer formulations, photosensitizer concentration, pre-irradiation and irradiation optimal time, as well as energy dosage used to make much more trustworthy conclusions. The present results are in agreement with previous reviews [7,10,24] that found a positive effect of adjunctive aPDT; however, that systematic reviews did not include very recent *in vivo* clinical trials studies. Contrary to the present study, that reviews had narrative approaches and the included studies were not analyzed systematically; therefore, definitive conclusions cannot be drawn.

5. Conclusion

Current systematic review and meta-analysis showed that although the aPDT parameters may vary from one study to the next, all RCTs found a reduction in microbial load with adjunctive use of aPDT. Therefore, use of adjunctive aPDT to conventional chemo-mechanical debridement of infected root canal system provides additional benefits; however, further high-quality RCTs focused on the standardized aPDT parameters and high methodological quality, possibly CONSORT and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [29] based, are needed.

Ethical approval

Not required. The manuscript does not contain clinical studies or patient data.

Conflict of interest

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

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