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Effect of antimicrobial photodynamic therapy and laser alone as adjunct to mechanical debridement in the management of halitosis: A systematic review

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Objective: The aim of the present study was to assess the efficacy of laser therapy (LT) and antimicrobial photodynamic therapy (aPDT) as adjunct to mechanical debridement (MD) on the management of halitosis. **Data Sources:** In order to address the focused question "Is MD with adjunct LT and/or aPDT more effective in the management of halitosis compared with MD alone?" an electronic search without time or language restrictions was conducted up to January 2017 in indexed databases using the combination of different key words including photochemotherapy, lasers, light, photodynamic therapy, halitosis, and bad breath. The exclusion criteria included qualitative and/or quantitative reviews, case reports, case series, commentaries, letters to the editor, interviews, and updates. **Results:** Six randomized control trials were included and processed for data extraction. Results from all studies reported that MD with adjunct LT or aPDT is more effective in reducing halitosis and/or volatile sulfur compounds concentration associated with oral conditions compared with MD alone. One study reported a significant reduction in bacterial colony forming units on the dorsum of the tongue among patients with coated tongue receiving MD with aPDT compared with MD alone. **Conclusion:** The efficacy of aPDT and/or LT on halitosis management remains unclear. Further well-designed randomized clinical trials assessing the efficacy of mechanical debridement with LT or aPDT on the halitosis treatment are needed. *(Quintessence Int 201#;##:1–9; doi: 10.3290/j.qi.a38264)*

Key words: halitosis, lasers, periodontal disease, photochemotherapy, photodynamic therapy

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Halitosis (also known as bad breath, fetor oris, and oral malodor) is defined as an unpleasant or offensive odor emanated from the oral cavity or hollow cavities of the sinuses, nose, and pharynx.[1,2] Clinically, halitosis can be classified into three groups: real or genuine halitosis, pseudohalitosis, and halitophobia.[3] The etiologic factors associated with genuine halitosis can be systemic or local. Systemic conditions such as gastrointestinal disorders (infection by *Helicobacter pylori*), infections in the respiratory system (including tonsillitis, sinusitis, and postnatal drip), and renal conditions account for

approximately 10% of halitosis cases;[4-6] whereas, local factors, which comprise up to 90% of halitosis cases, are associated with intraoral conditions such as poor oral hygiene, coated tongue, periodontal disease, insufficient salivary flow, and stomatitis.[1,7,8] Anaerobic gram-negative bacteria (such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *Treponema denticola*, and *Tannerella forsythia*) present in the oral cavity are capable to break down salivary proteins and metabolize amino acids (such as methionine and cysteine) in malodorous volatile sulfur compounds (VSCs) including hydrogen sulfide (H_2S), and methyl mercaptan or methanethiol (CH_3SH).[9-12] It has been estimated that approximately 80% of the population has experienced transient halitosis (for example, on waking up);[13,14] whereas, between 25% and 50% of the population is affected from permanent halitosis, representing a negative impact in the individual's social interactions, self-esteem, and quality of life.[1,10]

A variety of methods have been proposed for the management of halitosis. These include mechanical debridement (MD) of the oral biofilm (scaling and root planing [SRP], scrapers), masking agents (chewing gums, candies), and antiseptic mouthwashes (chlorhexidine, triclosan, chlorine dioxide);[1,15-18] however, the effectiveness of active ingredients in oral healthcare products is only short term in reducing microbes and their substrates.[19] Moreover, the effectiveness of active ingredients in oral healthcare products is dependent on their concentration, and above a certain concentration the ingredients can have unpleasant side effects.[19] Laser therapy (LT) involves the intensification of electromagnetic fields excited by external source of energy. The mechanism of action of LT includes biostimulatory, anti-ablation, and anti-infective (instant suppression of pathogenic bacteria) effects.[20] LT has been widely used as adjunct to SRP for the treatment of periodontal disease.[21-23] Similarly, antimicrobial photodynamic therapy (aPDT) is a modern disinfection protocol that has been used to disinfect dental implants, teeth surfaces, and acrylic dentures.[24-28] aPDT involves interactions between a light source (630 to 880 nm wavelength) and a photosensitizer such as methylene blue or toluidine blue. The resulting reaction produces reactive oxygen species that have a bactericidal effect.[29] To the present authors' knowledge from indexed literature, a limited number of studies[30-35] have assessed the efficacy of LT and/or aPDT as an adjunct to MD in the management of halitosis. In vitro results by Rai et al[12] demonstrated that aPDT is effective in reducing the number of oral microbes associated with VSCs production compared with LT alone. Similarly, da Mota et al[32] reported a statistically significant reduction in bacterial colony forming units (CFU) on the dorsum of the tongue among patients with coated tongue receiving MD with aPDT compared with MD alone. Dereci et al[33] reported that MD with adjunct LT was more effective at reducing VSCs levels in patients with halitosis compared with MD alone. Similar results were reported by Betsy et al[30,31] and Lopes et al.[35] To the present authors' knowledge from indexed literature, a systematic review of studies assessing the efficacy of LT and aPDT as adjunct to MD on the management of halitosis is yet to be reported. With this background, the aim of the present systematic review was to assess the efficacy of LT and aPDT as adjunct to MD on the management of halitosis.

DATA SOURCES

Focused question

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this systematic review.[36] A specific question was developed according to the Participants, Interventions, Control, and Outcomes (PICO) format. The addressed focused question was "Is MD with adjunct LT and/or aPDT more effective in the management of halitosis compared with MD alone?"

Eligibility criteria

A study was considered eligible for inclusion if it met the following criteria:

- randomized controlled clinical trials
- patients diagnosed with halitosis
- presence of control group (patients receiving MD without adjunctive LT or aPDT)

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- interventions evaluating efficacy of LT and/or aPDT as adjunctive therapy to MD.

The exclusion criteria were:

- qualitative and/or quantitative reviews
- laboratory (in vitro) and experimental (animal models) studies
- case reports and case series
- commentaries, letters to the editor, interviews, updates, and electronic posters
- studies where the intervention group received LT or aPDT without previous MD.

Literature search protocol

The international database of Prospectively Registered Systematic Reviews in Health and Social Care (PROSPERO) and the Cochrane Register of Systematic Reviews were searched by one author (SVK) in January 2017, and the search results showed no existing or current review protocols assessing the efficacy of LT and/or aPDT in the management of halitosis. In order to identify studies relevant to the focused question, two authors (SVK and VRM) conducted a structured and logical electronic search without time or language limitations up to January 2017 using PubMed (National Library of Medicine), Google Scholar, Scopus, EMBASE, and MEDLINE (OVID) databases. The following Medical Subject Headings (MeSH) were used:

1. photochemotherapy
2. lasers
3. light
4. halitosis.

Other related non-MeSH terms were used in the search strategy to detect additional articles. These included:

5. volatile sulfur compounds
6. photodynamic therapy
7. fetor oris
8. malodour
9. bad breath.

These keywords were used in the following combinations:

a. 1 or 2 or 3 or 6 and 4
b. 1 or 2 or 3 or 6 and 5
c. 1 or 2 or 3 or 6 and 7
d. 1 or 2 or 3 or 6 and 8
e. 1 or 2 or 3 or 6 and 9.

To minimize the potential for reviewer bias, titles and abstracts of studies identified using the above-described protocol were independently screened by two reviewers (SVK and VRM) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of original studies were hand-searched to identify any articles that could have been missed during the initial search. Hand-searching of the following journals was performed: Journal of Breath Research, Photomedicine and Laser Surgery, Journal of Lasers in Medical Science, Journal of Photochemistry and Photobiology, and Photodiagnosis and Photodynamic Therapy. Any disagreements among the authors in the study selection were resolved via discussion and consensus. Cohen's kappa value[37] was used to determine the inter-reviewer reliability between the two reviewers. The kappa coefficient for inter-reviewer agreement was 0.9.

Quality assessment

In an attempt to increase the strength of the present systematic review, the studies that were included underwent a quality assessment following the revised recommendations of the CONSORT statement for the evaluation of randomized control trials.[38] An overall estimation of plausible risk of bias was obtained for each selected study following the Cochrane collaboration risk of bias tool.[39]

RESULTS

Study selection

In total, 257 potential articles were initially identified, out of which 256 were identified through electronic database searching and one with hand-searching. After title and abstract screening, 239 publications that did not fulfill the eligibility criteria were excluded. In the second step, 12 more articles were excluded for the following reasons: did not have a control group (3); were case series (2), electronic poster (1), experimental studies

(4) or study protocols (1); or LT and aPDT were applied without mechanical debridement (1). A total of six studies[30-35] were included in the present systematic review and processed for data extraction (Fig 1). In the present study, only a qualitative analysis was performed since the significant heterogeneity among the studies did not allow pooling of the results and quantitative analysis.

General characteristics

All studies[30-35] were conducted under university settings between 2008 and 2016, in the following countries: Brazil, India, and Turkey. All studies[30-35] were randomized control trials with a parallel design. The number of study participants among the studies ranged between 45 and 90 individuals, with age ranging between 12 years and 65 years, with the mean (± standard deviation [SD]) age ranging between 13.5 ± 0.86 years and 43.83 ± 5.27 years. In total, 389 patients were included, 198 female and 191 male. In five studies,[30,32-35] systemically healthy individuals were included and confounding variables including pregnancy and lactation, antibiotics medication, and/or recent periodontal treatment were assessed. Two studies[30,34] excluded smokers, whereas three studies[32,33,35] did not clearly report whether smokers were included or excluded. In the study by Betsy et al,[31] the confounding variables remained unclear.

Four studies[30-32,35] assessed the efficacy of aPDT in the treatment of halitosis, out of which two studies[30,31] assessed the role of aPDT as adjunct therapy to SRP in the management of halitosis associated with chronic periodontitis (CP), and two studies[32,35] reported the efficacy of aPDT with and without MD of coated tongue for the treatment of halitosis. Two studies[33,34] reported the efficacy of SRP with adjunct LT in the treatment of halitosis associated with CP compared with SRP alone. In all studies,[30-35] the follow-up period ranged between 1 hour and 6 months (Table 1).

Methods for the assessment of halitosis

In two studies,[30,31] the diagnosis of halitosis was self-reported using the hand on mouth technique, and graded using the Likert scale (scale of 1 to 5):

1. strongly disagree
2. disagree
3. neither agree nor disagree
4. agree
5. strongly agree.

Two studies[32,35] diagnosed halitosis using cysteine challenge (levels of $H_2S \geq 112$ ppb) with portable gas chromatograph (Table 2). Dereci et al[33] and Kara et al[34] used a portable sulfur monitor (or halimeter) to detect VSCs concentration. In the study by da Mota et al,[32] microbiologic collection on the dorsum of the tongue was performed pre- and postoperatively to assess the bacterial count. In one study,[34] an organoleptic judge graded the halitosis levels on a 0 to 5 scale:

0. no appreciable
1. barely noticeable
2. slight but clearly noticeable
3. moderate
4. strong
5. extremely strong.

Three studies[32,33,35] instructed the patients to avoid foods with strong spices and garlic, alcohol, smoking, and antiseptic mouthwashes, 1 or 2 days before the breath readings; whereas, in three studies,[32,34,35] the participants were instructed not to use scented cosmetic products (such as deodorant, perfume, aftershave) prior to the breath readings. In four studies,[32-35] the participants were instructed not to eat, drink, or use mints, gum, and/or oral hygiene products 1 to 2 hours prior to the reading.

Laser and photosensitizer parameters

All aPDT studies[30-32,35] used diode lasers with wavelengths ranging between 655 nm and 660 nm and a power between 0.05 W and 1 W. Two studies[30,31] used optic fiber with 0.5 mm diameter, whereas two studies[32,35] did not report the optic fiber diameter. All the aPDT studies[30-32,35] were conducted in a single session, with an irradiation time ranging between 60 seconds and 90 seconds per area or tooth. In all studies,[30-32,35] methylene blue with concentrations ranging between 0.05 mg/mL and 10 mg/mL was used as photosensitizer. The photosensitization period prior to laser application ranged between 1 minute and 5 minutes.[30-32,35]

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Table 1 General characteristics of included studies

Subject	Study (country, year)	Sample size (sex F/M)	Mean age (range, y)	Study groups (n)	Cause of halitosis	Halitosis diagnosis method	Mean follow-up	Main outcomes
Studies for antimicrobial photodynamic therapy	Betsy et al[30] (India, 2014)	88 (51/37)	(18–65). Group 1, 38.4 ± 9.6; Group 2, 40.8 ± 8.3	Group 1, 44 control (SRP); Group 2, 44 SRP + aPDT	Chronic periodontitis	Self-reported (hand on mouth technique)	Up to 6 months	Halitosis was significantly lower in Group 2 compared with Group 1 after 1 month follow up.
	Betsy et al[31] (India, 2016)	90 (51/39)	39.6 ± 8.7. Group 1, 38.4 ± 9.6; Group 2, 40.8 ± 8.3	Group 1, 44 control (SRP); Group 2, 44 SRP + aPDT	Chronic periodontitis	Self-reported (hand on mouth technique)	Up to 6 months	Halitosis was significantly lower in Group 2 compared with Group 1 after 1 month follow up.
	da Mota et al[32] (Brazil, 2016)	46 (24/22)	14.80 ± 2.50 (12–19)	Group 1, 15 aPDT; Group 2, 15 tongue scraper; Group 3, 15 tongue scraper + aPDT	Coated tongue	Cysteine challenge with gas chromatography ($H_2S \geq 112$ pb), microbiologic analysis	1 h, 7 d	H_2S concentration was significantly lower in Group 3 compared with Group 2 after 1 h of treatment. Bacterial CFU was significantly lower in Group 1 compared with Group 2.
	Lopes et al[35] (Brazil, 2016)	45 (20/25)	(13–18). Group 1, 13.5 ± 0.86; Group 2, 14 ± 1.46; Group 3, 14.35 ± 1.71	Group 1, 16 aPDT; Group 2, 15 tongue scraper; Group 3, 14 tongue scraper + aPDT	Coated tongue	Cysteine challenge with gas chromatography ($H_2S \geq 112$ pb, $CH_3SH > 26$ ppb and $CH_3SCH_3 > 8$ ppb)	1 h	H_2S concentration was significantly lower in Group 3 compared with Groups 1 and 2.
Studies for laser therapy	Dereci et al[33] (Turkey, 2016)	60 (29/31)	43.7 ± 3.1	Group 1, 30 SRP; Group 2, 30 SRP + HLT	Chronic periodontitis	VSCs with a sulfur monitor	Up to 6 months	VSCs was significantly lower in Group 2 compared with roup 1 after 3 and 6 months follow-up.
	Kara et al[34] (Turkey, 2008)	60 (23/37)	Group 1, 41.90 ± 5.09; Group 2, 40.08 ± 3.91; Group 3, 43.83 ± 5.27	Group 1, 12 SRP; Group 2, 14 HLT + povidone-iodine; Group 3, 11 SRP + HLT	Chronic periodontitis	Organoleptic (judge). VSCs with a sulfur monitor	Up to 4 weeks	VSCs and organoleptic scores were significantly lower in Groups 1 and 3 compared with Group 2.

aPDT, antimicrobial photodynamic therapy; CFU, colony forming units; CH_3SCH_3, dimethyl sulfide; CH_3SH, methyl mercaptan; F, female; HLT, high-intensity laser therapy; H_2S, hydrogen sulfide; M, male; SRP, scaling and root planing; VSC volatile sulfur compound.

In LT studies,[33,34] high-intensity lasers (Er,Cr:YSGG or Nd:YAG) were used. The laser wavelengths used in the study by Kara et al[34] was 1,064 nm. The wavelengths used by Dereci et al[33] remained unclear. In these primary studies,[33,34] the power ranged between 0.05 W and 2 W; whereas, the frequency of LT ranged from one to three applications.

Main outcomes

Two aPDT studies[30,31] showed that MD with adjunct aPDT was more effective in reducing self-reported halitosis values compared with MD alone. Two aPDT studies[32,35] reported that H_2S levels were significantly lower when MD was used with adjunct aPDT to treat coated tongue compared with MD alone. One study[32] reported

Table 2 Laser and photosensitizer parameters of included studies

Subject	Study	Type of laser	Optic fiber diameter (mm)	Wave-length (nm)	Energy (J)	Energy fluence (J/cm²)	Power (W)	Power density (mW/cm²)	Duration of laser applica-tion (s per area)	Number of appli-cations (time interval)	Type of PS (con-centra-tion in mg/mL)	Duration of PS applica-tion
Antimicrobial photo-dynamic therapy	Betsy et al[30]	Diode	0.5	655	NA	NA	1	60	60	1	MB (10)	3 min
	Betsy et al[31]	Diode	0.5	655	NA	NA	1	60	60	1	MB (10)	3 min
	da Mota et al[32]	Diode	NA	660	9	320	0.1	3,537	90	1	MB (0.05)	5 min
	Lopes et al35	Diode	NA	660	54	317.43	0.1	3,527	90	1	MB (0.05)	5 min
Laser therapy	Dereci et al33	Er,Cr:YSGG	NA	NA	NA	NA	1.5	NA	NA	3 (base-line, 2 d, 7 d)	NA	NA
	Kara et al34	Nd:YAG	NA	1,064	0.1	NA	2	NA	90	1	NA	NA

MB, methylene blue; NA, not available; PS, photosensitizer.

significant reduction in bacterial CFU on the dorsum of the tongue among patients with coated tongue receiving MD with aPDT compared with MD alone.

LT studies[33,34] reported that MD with adjunct LT was more effective in reducing VSCs concentration and/or organoleptic scores in patients with halitosis compared with MD alone and LT alone.

Quality assessment

Seven specific criteria were evaluated during the quality assessment:

A. sample size calculation or the minimum number of participants required to detect a significant difference among compared groups (grading: 0 = unclear; 1 = reported but not confirmed; 2 = reported and confirmed)
B. randomization and allocation concealment methods (grading: 0 = clearly inadequate; 1 = possibly adequate; 2 = clearly adequate)
C. clear definition of inclusion and/or exclusion criteria (grading: 0 = no; 1 = yes)
D. complete follow up (grading: 0 = no or unclear; 1 = yes)
E. experimental and control groups comparable at study baseline (grading: 0 = no; 1 = unclear; 2 = adequate)
F. presence of masking (grading: 0 = no; 1 = unclear; 2 = yes)
G. appropriate statistical analysis (grading: 0 = no; 1 = unclear; 2 = yes).

After determining the scores, an overall estimation of risk of bias (low, moderate, or high) was estimated for each selected study. A low risk of bias was estimated when all the criteria were met; those studies which partly met one or more criteria were estimated as moderate risk of bias; and the risk of bias was estimated as high when one or more criteria were not met.[39]

Quality assessment identified that in general, comparability of control and test group at baseline for halitosis, recruitment of the patients, and appropriate statistical analysis were adequately performed in these studies. Randomization method was reported in four studies,[30,33-35] including block randomization using sealed envelopes,[30] randomization based in the order of arrival,[35] and random computer number generation.[33,34] Two studies[31,32] did not report the method used for randomization. Three studies[30,31,35] described

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Table 3 Quality assessment of included studies following CONSORT statement and Cochrane collaboration risk of bias tool

Study	A (0–2)	B (0–2)	C (0–1)	D (0–1)	E (0–2)	F (0–2)	G (0–2)	Estimated risk of bias
Betsy et al[30]	2	2	1	1	2	2	2	Low
Betsy et al[31]	2	1	0	1	2	2	2	High
da Mota et al[32]	1	1	1	1	2	1	2	High
Lopes et al[35]	2	2	1	1	2	1	2	Moderate
Dereci et al[33]	1	2	1	1	2	2	2	Moderate
Kara et al[34]	1	2	1	1	2	1	2	High

A, sample size calculation (minimum number of participants required to detect a significant difference among compared groups); B, randomization and allocation concealment methods; C, clear definition of inclusion and/or exclusion criteria; D, complete follow up; E, experimental and control groups comparable at study baseline; F, presence of masking; G, appropriate statistical analysis.

the power and sample size calculation. Risk of bias was regarded as low in one study[30] since this study met all the criteria. Studies by Dereci et al[33] and Lopes et al[35] were graded as moderate risk of bias because they partly met one criterion (unclear sample size calculation and non-presence of masking, respectively); the remaining three studies[31,32,34] were catalogued as high risk of bias because one or more criteria were not met. Quality assessment of the included studies is summarized in Table 3.

DISCUSSION

To the present authors' knowledge from indexed literature, this is the first study that systematically reviewed the efficacy of MD with and without adjunct LT or aPDT on the management of halitosis. Results from all the studies[30-35] reported that MD with adjunct LT or aPDT was more effective in reducing halitosis and/or VSCs levels associated with oral conditions compared with MD alone. It is therefore tempting to speculate that MD with adjunct aPDT or LT is a potential therapeutic strategy for the management of halitosis. However, several confounding factors seem to have influenced the reported results.

Firstly, the included studies[30-35] had a discrepancy in the methods utilized to assess and diagnose halitosis. In nearly 34% of the studies,[30,31] halitosis was diagnosed using the hand on mouth technique (self-perception). This method presents several limitations including high subjectivity, lack of quantification and reproducibility, and the saturation of the nose.[8] Moreover, two studies[33,34] that assessed VSCs levels (an objective and quantifiable measurement) used portable volatile sulfide monitors as diagnostic tools. These devices are capable of detecting VSCs such as H_2S; however, it has been reported that portable volatile sulfide monitors present inaccurate detection of CH_3SH levels compared with other diagnostic methods such as gas chromatography.[8,40] Therefore, additional well-designed clinical studies using reliable diagnostic tools capable of detecting accurately different VSCs associated with halitosis are needed.

Secondly, it is noteworthy that in approximately 84% of the included studies,[30-32,34,35] LT or aPDT was performed once. The authors of the present systematic review perceive that the primary factor that should determine the frequency of LT or aPDT is the severity of halitosis. It is hypothesized that patients with higher concentrations of VSCs require multiple treatments using LT or aPDT compared to individuals having significantly lower concentrations of VSCs. Therefore further studies with particular emphasis on the frequency of LT or aPDT in relation to the concentration of VSCs are needed.

Another factor that may have influenced the reported results is the follow-up duration. The maximum follow-up duration in the included studies[30-35] in the present systematic review was 6 months. The long-term efficacy of LT and aPDT in the management of halitosis remains unclear. It is highlighted that LT and aPDT should be accompanied with regular follow-up and reinforcement of oral hygiene and patient education. Furthermore, halitosis has been associated with high intake of fast food, instant noodles, and low intake of fruits of vegetables.[41] The present systematic review was based upon results from primary studies conducted in three countries: Brazil, India, and Turkey. Therefore, there might be some bias as to the findings from this study, related to the potential diet differences present from the types of foods customarily consumed among these three countries. More multi-center and well-designed studies are needed.

It is pertinent to mention that LT studies[33,34] used high-intensity lasers (Nd:YAG and Er,Cr:YSGG). Although high-intensity lasers have shown beneficial effects in the treatment of oral diseases,[42,43] the possibility of soft tissue damage such as necrosis (due to overheating of tissues) cannot be disregarded.[44]

CONCLUSION

The efficacy of aPDT and/or LT on the halitosis management remains unclear. Further well-designed randomized clinical trials assessing the efficacy of mechanical debridement with LT or aPDT on the halitosis treatment are needed.

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