[DOI]10.12016/j.issn.2096-1456.2021.08.010

·综述·

光动力疗法在牙周炎治疗领域的应用研究进展

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【摘要】 牙周炎是一种以细菌为始动因素的慢性炎症性疾病，高危致病菌及其毒力因子可通过改变局部组织细胞正常的代谢活动打破牙周微环境的平衡，促进炎症的发生发展。研究表明，由于牙体解剖结构的复杂性和机械清创的局限性，C级或Ⅲ/Ⅳ期牙周炎患者仅行洁治术和刮治术不一定能达到预期的治疗效果。光动力疗法（photodynamic therapy，PDT）具有低毒性、高效杀菌、不引起细菌耐药性、利于组织愈合等优点，是一种可用于牙周菌斑控制的理想疗法。但是它无法清除龈下的结石，仍不能代替机械治疗来初步控制牙周的炎症，所以临床中多选用近红外低能量光配合传统光敏剂进行牙周辅助治疗。在定期进行牙周维护治疗时，单独应用可减轻患者的敏感程度，有效控制菌斑，但其效果会受到患者牙周炎症程度、光敏剂浓度和种类、光源能量大小等的影响。随着材料学研究的日趋深入，光敏剂的氧产物催生性能、靶向结合细菌性能及PDT的杀菌消炎性能也显著优化。同时，与不同分期、分级的牙周炎病情相匹配的PDT参数仍需进行长期、大样本的深入研究。

【关键词】 牙周炎；　牙周维护治疗；　牙周菌斑控制；　牙周机械治疗；　光动力疗法；　光源；　光敏剂；　氧气；　杀菌
【中图分类号】 R78　**【文献标志码】** A　**【文章编号】** 2096-1456（2021）08-0562-05
开放科学（资源服务）标识码（OSID）
【引用著录格式】 尹馨，任秀云. 光动力疗法在牙周炎治疗领域的应用研究进展[J]. 口腔疾病防治, 2021, 29(8): 562-566. doi: 10.12016/j.issn.2096-1456.2021.08.010.

Research progress on the application of photodynamic therapy in periodontal treatment

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【Abstract】 Periodontitis is a chronic inflammatory disease that is initiated by bacteria. Pathogens and their virulence factors alter normal cellular metabolic activity and deteriorate periodontal microconditions. Owing to the complexity of tooth structure and the limitation of conventional treatment, we may not live up to all patients' expectations, especially those with grade C and stage Ⅲ or Ⅳ periodontitis. With the advantages of bactericidal effects, high safety, inhibition of bacterial drug resistance and promotion of tissue healing, photodynamic therapy (PDT) seems to be an ideal technology in periodontal treatment. However, it cannot remove subgingival stones and still cannot replace mechanical treatment to preliminarily control periodontal inflammation. Therefore, near-infrared low-energy light combined with traditional photosensitizers is mostly used in clinical periodontal adjuvant treatment. In periodontal maintenance treatment on a regular basis, a single application can also reduce the sensitivity of patients and effectively control plaque, but its effect will be affected by the degree of periodontal inflammation, the concentration and type of photosensitizer, the energy of the light source, etc. With the further development of material science, the performance of photosensitizers to accelerate oxides and target bacteria will be optimized. In the future, parameters of PDT need to be designed in large-scale studies in accord with different stages and grades of periodontitis.

【收稿日期】 2020-10-04；　**【修回日期】** 2021-2-25
【基金项目】 山西省"1331"工程重点创新团队建设计划（TD201809）；中央引导地方科技发展资金项目(YDZX20201400001131)；山西医科大学口腔医院科研课题（KY201705）
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【Key words】 periodontitis; supportive periodontal therapy; dental plaque control; periodontal mechanical therapy; photodynamic therapy; light source; photosensitizer; oxygen; bactericidal
J Prev Treat Stomatol Dis, 2021, 29(8): 562-566.
【Competing interests】 The authors declare no competing interests.
This study was supported by the grants from Shanxi Key Innovative Research Team in the "1331 Project" (No. TD201809); The Central Government Guides Local Science and Technology Development Fund Projects(No. YDZX20201400001131); Scientific Project of Shanxi Medical University Hospital of Stomatology (No. KY201705).

牙周炎是以牙支持组织丧失为特征的慢性炎症性疾病，高危致病菌及其毒力因子可改变局部组织细胞的氧化还原状态影响正常的代谢活动[1]。龈上洁治术+龈下刮治术+根面平整术(scaling and root planing，SRP)是临床中牙周基础治疗的核心[2]。由于洁治器和刮治器的作用效果会随着袋深的增加受到根分叉、根面凹陷等解剖结构的限制，所以常对C级或Ⅲ/Ⅳ期牙周炎患者的局部及全身应用抗菌药物作为SRP的补充[3]。但是抗生素难以在牙周袋内达到预期浓度，全身应用后极易引起菌株耐药性，所以学者们都致力于寻找一种更为理想的辅助疗法。

光动力疗法(photodynamic therapy，PDT)是医药学、光物理学和光化学等学科共同发展的产物，由光源、无毒光敏剂和氧气三个要素组成，其作用机制是：在氧气存在的条件下，用特定波长的光激活光敏剂，使其从低能量基态转变为高能量三线态，随后与氧气反应，产生具有细胞毒性的单线态氧和其他活性氧物质，引起靶细胞的凋亡或坏死[4]。1900年，Oscar Raab偶然发现吖啶橙染色的草履虫受到光照时死亡的现象。1904年，Jodlbaner和Von Tappeiner通过实验证明了氧气是这种光介导的杀菌效应所必需的物质之一，并首次将这种反应用"photodynamic"一词定义。20世纪中期随着抗生素产业的飞速发展，有关PDT的研究停滞不前[5]。直到1978年，Dougherty等[6]用PDT治愈了上百例肿瘤才将其重新带入人们的视野，后来PDT逐渐应用到皮肤病和妇科病的临床治疗中[7]。作为一种冷光化学反应，PDT在发挥良好抗菌效能的同时不会引起耐药性，是一种较为理想的牙周辅助治疗方法。

1　PDT的三要素

1.1　光源

光源是PDT的重要组成部分，激光具有单色性好、方向性高等特点，一般将其作为PDT的激发光源。人体软组织会吸收光能，降低光敏剂的激发程度，但是它在近红外光谱区域具有低吸收特性，因此临床中多采用630～700 nm的红色光进行照射，传导深度达软组织表面下方0.5～1.5 cm[8]。二极管激光的波长介于630～980 nm，能够在牙周袋内高效激活光敏剂，达到消灭牙周致病菌的目的，是临床中较为常用的光源。近年来，发光二极管(light-emitting diodes，LED)因仪器便于携带、使用成本较低和性能稳定等特点，也被用作新的光源装置[9]。

1.2　光敏剂

光敏剂是一种在光化学反应中吸收能量但不被消耗的介质，早期研发的第一代光敏剂为血卟啉衍生物，由于它对红光的吸收能力弱，作用深度有限，单线态氧产量低，易引起皮肤的光过敏反应，在医学中的应用受到了限制。改进后的第二代光敏剂(5-氨基酮戊酸、二氢卟吩E6、亚甲基蓝和甲苯胺蓝)在纯度、活性、组织选择性和产生单线态氧的能力方面均优于第一代，较符合对理想光敏剂的要求。亚甲基蓝和甲苯胺蓝属于吩噻嗪类染料，表面带有正电荷，在进行牙周治疗时，可优先选择与表面带有负电荷的牙周致病菌相结合[10]，有效增强灭菌效果。第三代光敏剂由第二代光敏剂与低密度脂蛋白、单克隆抗体和生长因子受体等生物活性物质交联后获得，主要用于增强与肿瘤组织的亲和力[11]，在牙周治疗中很少应用。

1.3　氧气

氧气是PDT反应中生成单线态氧和活性氧(reactive oxygen species，ROS)的底物，这两类氧产物的细胞毒性体现在不仅能损伤细菌的细胞壁和细胞膜，还可快速氧化内部的蛋白质、脂质、核酸等生物大分子。单线态氧在杀菌效应中发挥主导作用[7]，其生命周期短，不超过0.3 μs，有效作用范

围局限，不超过0.05 μm，对周围正常组织几乎无影响[12]。ROS可诱导牙周炎症组织中广泛浸润的巨噬细胞凋亡，减少牙槽骨吸收[13]。但炎症部位的巨噬细胞有促炎型和抗炎型两种[14]，ROS引起凋亡的巨噬细胞表型尚不清楚。

2　PDT应用于牙周的基础研究

1992年，Wilson等[15-16]首次证实了在亚甲基蓝、甲苯胺蓝等光敏剂的配合下，低能量氦氖激光能够有效杀灭以游离态和生物膜形式存在的牙龈卟啉单胞菌、伴放线聚集杆菌和福赛坦氏菌等牙周致病菌，提示PDT可能是一种适用于临床中牙周局部治疗且能替代抗生素的疗法。Alvarenga等[17]用亚甲基蓝处理伴放线聚集杆菌的生物膜，660 nm的二极管激光照射5 min后用扫描电镜观察，发现细菌量减少了99.85%，原有的生物膜结构松解。Decker等[18]将6种混合厌氧菌群用亚甲基蓝/甲苯胺蓝+LED/二极管激光组成的PDT进行处理，对生物膜中细菌的杀灭效果也很好。Su等[19]对牙周炎大鼠局部应用甲苯胺蓝-635 nm二极管激光介导的PDT后，不仅组织局部浸润的中性粒细胞数目减少，核因子-κB受体活化因子配体（receptor activator of NF-κB ligand，RANKL）的表达和牙槽骨吸收量也显著低于对照组，同时骨保护素（osteoprotegerin，OPG）的表达高于对照组，此研究中PDT在减轻局部免疫炎症反应的同时，还起到了抑制破骨细胞活动、加速骨形成的功能，在临床中对改善C级或Ⅲ/Ⅳ期牙周炎患者的预后具有重要意义。

稀土掺杂上转换纳米粒子（upconverting nanoparticles，UCNPs）是目前最具代表性的光转换材料，其光学特性稳定，激发光源是PDT常用的近红外光[3]。UCNPs可有效地将近红外光转换为紫外光，激发组织深处的氧化钛颗粒产生ROS，发挥杀菌作用。因此对于C级或III、IV期牙周炎的微环境来说，UCNPs负载光敏剂可到达更深、更为复杂的区域，较长时间发挥作用，持续产生ROS杀灭致病菌。

3　PDT用于牙周的临床治疗

PDT辅助应用于牙周临床治疗疗效颇佳，特别对牙周炎病情严重复杂的患者具有较高的使用价值[20-24]。Cadore等[25]在对Ⅲ期牙周炎患者行常规SRP后2周内行4次PDT，术后3个月检查发现：PDT组的牙周袋探诊深度和附着丧失均显著改善（$P<0.05$），袋内红色复合体的比例下降，一些益于牙周健康的菌群数目增多，但是橙色复合体的数目不降反升，说明了龈下菌群开始重新定植，提示牙周炎患者应该定期进行牙周的维护治疗。由于维护阶段对深牙周袋多次刮治极易导致根面敏感、牙龈退缩等问题，辅助应用PDT是一种好的选择[26]。

对于伴有系统性疾病（肥胖、2型糖尿病等代谢综合征）的牙周炎患者，由于他们全身处于炎症状态，牙周症状通常较单纯牙周炎患者更严重，牙周治疗的预后也会受到影响。对这些患者辅助应用PDT后，不仅能降低深牙周袋的探诊深度和附着丧失、减轻出血情况[27]，还可改善全身肿瘤坏死因子-α、白细胞介素-6[28]、糖化血红蛋白[29]等的水平，阻止胰岛素抵抗的发生发展，降低患者并发心血管疾病的风险，维护全身的稳态。

种植体周围炎是导致种植失败的主要原因之一，以种植体周围黏膜炎症和进行性支持骨组织丧失为特征，其病因和病程与牙周炎相似，但种植体表面的复杂特性导致临床中使用传统的机械和药物治疗方式仍难以有效控制菌斑[30]。Wang等[31]对种植体周围炎患者辅助应用PDT，术后半年实验组在探诊深度、附着丧失等方面的改善均优于对照组。在种植过程对种植体上部结构的内表面多次应用PDT，能够有效杀灭内部的致病菌，防止种植体周围炎的发生[32]。而当植体周围炎发生时，PDT的配合能在提高临床疗效的同时避免引起细菌耐药性，对种植体周围炎的防治具有重要意义。

也有研究报告并未发现PDT对C级和Ⅲ/Ⅳ期牙周炎患者的病情有改善作用。Pourabbas等[33]对22例病情较重的患者进行彻底SRP后在实验组中局部应用PDT，3个月后对比实验组与对照组的复查结果未出现明显的差异。有循证医学文献也因PDT的临床疗效尚不显而对其持怀疑态度[34]。

综上所述，研究者不能否定PDT可能带来的益处，但还应考虑患者自身牙周炎症程度、免疫系统功能改变、应用PDT次数、激光照射时间和观察期较短等因素造成的影响。

4　总结与展望

PDT被多数研究证实具有杀菌性能好、安全性能高、避免抗生素不良反应、利于牙周组织愈合等

优点，但是目前尚无与不同分期、分级的牙周炎病情相匹配的PDT参数供临床中使用，未来需进行长期、大样本的深入研究。PDT的受用人群及使用时机需结合患者的牙周炎症程度及全身情况进行考量，C级及Ⅲ/Ⅳ期的牙周炎患者病情复杂，PDT仍难以替代机械治疗和手术治疗来控制炎症进程，但作为牙周辅助疗法其能够强化传统治疗方式的效果。牙周维护治疗阶段不失为应用PDT的良好时机，相较于超声器械，它能在不引起患者牙根面敏感症状的同时达到较好的菌斑控制效果。尤其是对伴发心脑血管疾病的患者而言，PDT能降低牙周干预时全身炎症标记物的浓度，维持血管内斑块的稳定性，在牙周治疗及维护治疗阶段均可应用。在未来的研究中，提高光敏剂与牙周致病菌的靶向结合性，发展可控的光敏化技术，评估并改善光敏剂的效能对于增加氧产物释放效率、放大PDT的杀菌效能具有深远意义。

【**Author contributions**】 Yin X wrote the article. Ren XY revised the article. All authors contributed to the article and approved the submitted version.

参考文献

[1] Gandhi KK, Pavaskar R, Cappetta EG, et al. Effectiveness of adjunctive use of low-level laser therapy and photodynamic therapy after scaling and root planing in patients with chronic periodontitis [J]. Int J Periodontics Restorative Dent, 2019, 39(6): 837-843. doi: 10.11607/prd.4252.

[2] Joseph B, Janam P, Narayanan S, et al. Is antimicrobial photodynamic therapy effective as an adjunct to scaling and root planing in patients with chronic periodontitis? a systematic review[J]. Biomolecules, 2017, 7(4): 79. doi: 10.3390/biom7040079.

[3] Qi M, Li X, Sun X, et al. Novel nanotechnology and near-infrared photodynamic therapy to kill periodontitis-related biofilm pathogens and protect the periodontium[J]. Dent Mater, 2019, 35(11): 1665-1681. doi: 10.1016/j.dental.2019.08.115.

[4] Donohoe C, Senge MO, Arnaut LG, et al. Cell death in photodynamic therapy: from oxidative stress to anti-tumor immunity[J]. Biochim Biophys Acta Rev Cancer, 2019, 1872(2): 188308. doi: 10.1016/j.bbcan.2019.07.003.

[5] Kessel D. Photodynamic therapy: a brief history[J]. J Clin Med, 2019, 8(10): 1581. doi: 10.3390/jcm8101581.

[6] Dougherty TJ, Kaufman JE, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumors[J]. Cancer Res, 1978, 38 (8): 2628-2635.

[7] Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy - mechanisms, photosensitizers and combinations[J]. Biomed Pharmacother, 2018, 106(106): 1098 - 1107. doi: 10.1016/j.biopha.2018.07.049.

[8] Gursoy H, Ozcakir-Tomruk C, Tanalp J, et al. Photodynamic therapy in dentistry: a literature review[J]. Clin Oral Investig, 2013, 17 (4): 1113-1125. doi: 10.1007/s00784-012-0845-7.

[9] Liu H, Daly L, Rudd G, et al. Development and evaluation of a low-cost, portable, LED-based device for PDT treatment of early-stage oral cancer in resource-limited settings[J]. Lasers Surg Med, 2019, 51(4): 345-351. doi: 10.1002/lsm.23019.

[10] Kikuchi T, Mogi M, Iichiro O, et al. Adjunctive application of antimicrobial photodynamic therapy in nonsurgical periodontal treatment: a review of literature[J]. Int J Mol Sci, 2015, 16(10): 24111-24126. doi: 10.3390/ijms161024111.

[11] Baskaran R, Lee J, Yang SG. Clinical development of photodynamic agents and therapeutic applications[J]. Biomater Res, 2018, 22: 25. doi: 10.1186/s40824-018-0140-z.

[12] Abrahamse H, Hamblin MR. New photosensitizers for photodynamic therapy[J]. Biochem J, 2016, 473(4): 347-364. doi: 10.1042/BJ20150942.

[13] Jiang C, Yang W, Wang C, et al. Methylene blue-mediated photodynamic therapy induces macrophage apoptosis via ROS and reduces bone resorption in periodontitis[J]. Oxid Med Cell Longev, 2019 (2): 1529520. doi: 10.1155/2019/1529520.

[14] Shapouri-Moghaddam A, Mohammadian S, Vazini HA, et al. Macrophage plasticity, polarization, and function in health and disease [J]. J Cell Physiol, 2018, 233(9): 6425 - 6440. doi: 10.1002/jcp.26429.

[15] Wilson M, Dobson J, Harvey W. Sensitization of oral bacteria to killing by low-power laser radiation[J]. Curr Microbiol, 1992, 25 (2): 77-81. doi: 10.1007/BF01570963.

[16] Dobson J, Wilson M. Sensitization of oral bacteria in biofilms to killing by light from a low-power laser[J]. Arch Oral Biol, 1992, 37 (11): 883-887. doi: 10.1016/0003-9969(92)90058-g.

[17] Alvarenga LH, Prates RA, Yoshimura TM, et al. Aggregatibacter actinomycetemcomitans biofilm can be inactivated by methylene blue-mediated photodynamic therapy[J]. Photodiagnosis Photodyn Ther, 2015, 12(1): 131-135. doi: 10.1016/j.pdpdt.2014.10.002.

[18] Decker EM, Bartha V, Von Ohle C. Improvement of antibacterial efficacy through synergistic effect in photodynamic therapy based on thiazinium chromophores against planktonic and Biofilm-Associated periodontopathogens[J]. Photomed Laser Surg, 2017, 35(4): 195-205. doi: 10.1089/pho.2016.4152.

[19] Su X, Zhuang D, Zhang Y, et al. Influence of photodynamic therapy on the periodontitis-induced bone resorption in rat[J]. Lasers Med Sci, 2020. doi: 10.1007/s10103-020-03126-8.

[20] Grzech-Leśniak K, Gaspirc B, Sculean A. Clinical and microbiological effects of multiple applications of antibacterial photodynamic therapy in periodontal maintenance patients. a randomized controlled clinical study[J]. Photodiagnosis Photodyn Ther, 2019, 27: 44-50. doi: 10.1016/j.pdpdt.2019.05.028.

[21] Derikvand N, Ghasemi SS, Safiaghdam H, et al. Antimicrobial photodynamic therapy with diode laser and methylene blue as an adjunct to scaling and root planning: a clinical trial[J]. Photodiagnosis Photodyn Ther, 2020, 31: 101818. doi: 10.1016/j.pdpdt.2020.101818.

[22] Sukumar K, Tadepalli A, Parthasarathy H, et al. Evaluation of combined efficacy of photodynamic therapy using indocyanine green photosensitizer and non-surgical periodontal therapy on clinical and microbial parameters in the management of chronic periodontitis subjects: a randomized split-mouth design[J]. Photodiagnosis Photodyn Ther, 2020,31, 101949. doi: 10.1016/j.pdpdt.2020.101949.

[23] Habashneh RA, Mashal M, Khader Y, et al. Clinical and biological effects of adjunctive photodynamic therapy in refractory periodontitis[J]. J Lasers Med Sci, 2019, 10(2): 139 - 145. doi: 10.15171/jlms.2019.22.

[24] Al-Khureif AA, Mohamed B, Siddiqui AZ, et al. Repeated application of photodynamic and antibiotic therapy as an adjunct to root surface debridement in patients with grade C and stage III or IV aggressive periodontitis[J]. Photodiagnosis Photodyn Ther, 2020, 29: 101610. doi: 10.1016/j.pdpdt.2019.101610.

[25] Cadore UB, Reis M, Martins S, et al. Multiple sessions of antimicrobial photodynamic therapy associated with surgical periodontal treatment in patients with chronic periodontitis[J]. J Periodontol, 2019, 90(4): 339-349. doi: 10.1002/JPER.18-0373.

[26] Franco T, Dos Santos A, Canabarro A. The effects of repeated applications of antimicrobial photodynamic therapy in the treatment of residual periodontal pockets: a systematic review[J]. Lasers Med Sci, 2019, 34(5): 855-863. doi: 10.1007/s10103-018-02703-2.

[27] Ivanaga CA, Miessi D, Nuernberg M, et al. Antimicrobial photodynamic therapy (aPDT) with curcumin and LED, as an enhancement to scaling and root planing in the treatment of residual pockets in diabetic patients: a randomized and controlled split-mouth clinical trial[J]. Photodiagnosis Photodyn Ther, 2019, 27(27): 388-395. doi: 10.1016/j.pdpdt.2019.07.005.

[28] Vohra F, Akram Z, Bukhari IA, et al. Short-term effects of adjunctive antimicrobial photodynamic therapy in obese patients with chronic periodontitis: a randomized controlled clinical trial[J]. Photodiagnosis Photodyn Ther, 2018, 21: 10-15. doi: 10.1016/j.pdpdt.2017.10.022.

[29] Elsadek MF, Ahmed BM, Alkhawtani DM, et al. A comparative clinical, microbiological and glycemic analysis of photodynamic therapy and Lactobacillus reuteri in the treatment of chronic periodontitis in type-2 diabetes mellitus patients[J]. Photodiagnosis Photodyn Ther, 2020, 29: 101629. doi: 10.1016/j.pdpdt.2019.101629.

[30] 孟焕新. 2018年牙周病和植体周病国际新分类简介[J]. 中华口腔医学杂志, 2019, 54(2): 73-78. doi: 10.3760/cma.j.issn.1002-0098.2019.02.001.
Meng HX. 2018 world new classification of periodontal and peri-implant diseases and conditions[J]. Zhonghua Kou Qiang Yi Xue Za Zhi, 2019, 54(2): 73-78. doi: 10.3760/cma.j.issn.1002-0098.2019. 02.001.

[31] Wang H, Li W, Zhang D, et al. Adjunctive photodynamic therapy improves the outcomes of peri-implantitis: a randomized controlled trial[J]. Aust Dent J, 2019, 64(3): 256-262. doi: 10.1111/adj.12705.

[32] Zhou LY, Shi JY, Yu Z, et al. The effect of photodynamic therapy on pathogenic bacteria around peri-implant sulcus and in the cavity between abutment and implant after healing phase: a prospective clinical study[J]. Lasers Surg Med, 2018, 50(5): 433-439. doi: 10.1002/lsm.22929.

[33] Pourabbas R, Kashefimehr A, Rahmanpour N, et al. Effects of photodynamic therapy on clinical and gingival crevicular fluid inflammatory biomarkers in chronic periodontitis: a split-mouth randomized clinical trial[J]. J Periodontol, 2014, 85(9): 1222-1229. doi: 10.1902/jop.2014.130464.

[34] Chambrone L, Wang HL, Romanos GE. Antimicrobial photodynamic therapy for the treatment of periodontitis and peri-implantitis: an American Academy of Periodontology best evidence review [J]. J Periodontol, 2018, 89(7): 783-803. doi: 10.1902/jop.2017.170172.

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