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· 临床研究 ·

抗菌光动力疗法辅助龈下刮治治疗慢性牙周炎 临床效果观察

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【摘要】 目的 探讨抗菌光动力疗法(antibacterial photodynamic therapy, aPDT)辅助龈下刮治和根面平整(scaling and root planing, SRP)治疗慢性牙周炎的临床效果。方法 本研究已通过单位伦理委员会审查通过, 并获得患者知情同意。研究采用随机、对照分口设计, 符合纳入标准的16例慢性牙周炎患者随机分为试验侧与对照侧。对照侧接受常规SRP, 试验侧SRP基础上联合aPDT治疗(SRP+aPDT)。记录治疗前(基线)、治疗后1个月、3个月和6个月时牙周探诊深度(probing depth, PD)、菌斑指数(plaque index, PLI)、出血指数(bleeding index, BI)和探诊出血(bleeding on probing, BOP)阳性位点占比(BOP%)。结果 13例患者完成了全部随访。对照侧356颗受试牙, 2 136个位点; 试验侧360颗受试牙, 2 160个位点。治疗前, 两侧基线水平各指标差异无统计学意义。在治疗后1个月、3个月和6个月时, 试验侧和对照侧的牙周临床指标PD、PLI、BI、BOP%相较于治疗前均有明显改善($P < 0.05$)。在各时间点, 与常规SRP相比, SRP+aPDT联合治疗侧PD、PLI和BI均有改善。SRP+aPDT联合治疗侧在治疗后3个月时BOP%和PLI的改善明显优于常规SRP侧($P < 0.05$)。结论 aPDT辅助治疗慢性牙周炎可以在早期更好地改善牙龈出血, 控制牙周炎症。

【关键词】 慢性牙周炎; 抗菌光动力疗法; 牙周基础治疗; 龈下刮治和根面平整; 探诊深度; 菌斑指数; 出血指数; 探诊出血

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【Abstract】 **Objective** To investigate the efficacy of antibacterial photodynamic therapy (aPDT) as an adjunct to subgingival scaling and root planing in the treatment of chronic periodontitis. **Methods** This study followed medical ethics guidelines, and informed consent was obtained from all patients. Sixteen patients were recruited for this randomized split-mouth controlled trial. The control group underwent subgingival scaling and root planing (SRP), while the experimental group received subgingival scaling and root planing plus aPDT treatment using Perowave[®] with a toluidine blue O solution photosensitizer. The probing pocket depth (PD), recession, plaque index (PLI), bleeding index (BI) and proportion of positive sites of bleeding on probing (BOP) (BOP%) at all sites were examined at baseline (before treatment) and at 1, 3 and 6 months after treatment. **Results** Follow-up was completed for 13 patients. On the control side, 356 teeth were tested at 2 136 sites. A total of 360 teeth on the test side and 2 160 sites were included in the study.

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Before treatment, there was no significant difference in the baseline indicators between the two groups. After treatment, both groups showed significant improvement in clinical parameters, including PD, PLI, BI, and BOP%, compared with baseline. At 3 months, the BOP% and PLI in the experimental group were significantly lower than those in the control group ($P < 0.05$). The improvement in BOP% and PLI in the experimental group was significantly greater than that in the control group 3 months after treatment ($P < 0.05$). **Conclusion** aPDT, as an adjuvant treatment to SRP for chronic periodontitis, can improve gingival bleeding and control periodontal inflammation in the early stage.

【Key words】 chronic periodontitis; antibacterial photodynamic therapy; periodontal initial therapy; scaling and root planing; probing depth; plaque index; bleeding index; bleeding on probing

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慢性牙周炎是一种由牙菌斑生物膜引起的多因素感染性疾病,是成年人失牙的主要原因,常采用全身或局部使用抗菌类药物辅助牙周治疗^[1-2],但是,长期使用抗生素可能引发耐药性菌株的出现并破坏正常的菌群平衡,从而导致更为复杂的感染问题。在这一背景下,牙周病学家和临床医师不断寻求能够提升基础治疗效果的辅助治疗方法。抗菌光动力疗法(antibacterial photodynamic therapy, aPDT)是一种新型无创控制感染的方法,其基本原理是靶体内的光敏剂受到响应波长的光照射时,产生以单线态氧为主的一系列活性氧物质(reactive oxygen species, ROS)。ROS可以与微生物的磷脂、核酸和蛋白质等生物大分子反应,损伤细菌结构或影响其功能^[3]。国内外很多研究评估了aPDT作为辅助手段对牙周炎的治疗效果,尽管很多研究显示aPDT的优势^[4-6],但临床研究的结果仍存在争议。本研究设计了一项前瞻性、随机对照试验,旨在评估aPDT辅助传统牙周机械治疗是否有额外的临床获益,为aPDT在牙周临床治疗中的应用提供科学依据。

1 资料和方法

本研究获得首都医科大学附属北京口腔医院伦理委员会的批准(CMUSH-IRB-KJ-PJ-2019-15),并在国家卫健委医学研究登记备案信息系统进行了备案。所有参与者均知情同意并签署研究知情同意书。

1.1 研究设计及样本量设计

本研究是一项采用自身对照分口式设计的单中心、单盲随机临床试验。一侧为常规龈下刮治

(对照侧),另一侧为常规龈下刮治+aPDT(试验侧)。两侧的设置预先随机生成,通过计算机设计随机分组表,把分组所得方案放入顺序的、不透明密闭信封中。使用样本量计算公式估算所需样本量。 $\alpha=0.05$ (I类错误), $\beta=0.1$ (II类错误),双侧检验, δ 是实验组与对照组之间探诊深度差值1 mm, sd 是0.8 mm。按照计算公式: $n=[(t_{\alpha} + t_{\beta})sd/\delta]^2$ 因此,计算得出13.45,失访率按20%计算,需要16人。

1.2 研究对象

2020年12月至2022年6月从首都医科大学附属北京口腔医院特诊特需科和牙周科就诊的慢性牙周炎患者中招募,纳入16例患者。

纳入标准:①成年患者(≥ 18 岁);②至少有18颗完全萌出的牙;③全口至少1/3以上位点牙周探诊深度(probing depth, PD) ≥ 5 mm和邻面附着丧失(attachment loss, AL) ≥ 2 mm;④每个象限有不少于1个邻面位点的PD ≥ 5 mm;⑤近6个月未进行牙周治疗;⑥近3个月未服用抗生素及免疫抑制剂。

排除标准:①患有糖尿病、心血管疾病和血液性疾病等全身系统性疾病及传染病;②患有精神疾病,无自主意识和行为能力者;③妊娠及哺乳期妇女或口服避孕药者;④服用抗凝剂等任何影响治疗的药物者;⑤吸烟、嗜酒及明显错颌畸形、开口呼吸者;⑥对亚甲基蓝过敏者。

1.3 治疗方案

对照侧治疗方案:对患者进行口腔卫生宣教及龈上洁治术。洁治术后1周在4%盐酸阿替卡因(含1:10万肾上腺素,碧蓝公司,法国)局部浸润麻醉下行超声龈下刮治和手工根面平整术。使用尖探针探查牙根面确认是否有残余牙石。使用3%

双氧水及生理盐水冲洗牙周袋。治疗后1个月、3个月及6个月随访,对所有患者开展口腔卫生宣教。1个月随访时对照侧行盐水冲洗。

试验侧治疗方案:在对照侧基础上,完成SRP后即进行aPDT治疗。将0.01%甲苯胺蓝注入PD ≥ 5 mm的牙周袋内1 min后,采用派威牙周激光治疗仪(波长660 nm,功率100 mW,半导体激光,郑嘉泰州生物科技有限公司,中国)每个PD ≥ 5 mm位点均照射1 min,生理盐水冲洗牙周袋。治疗后1、3、6个月随访,对患者开展口腔卫生宣教。1个月随访时试验侧再次进行aPDT维护治疗。

1.4 临床评价指标及资料收集

在基线(龈上洁治后1周,SRP治疗前)、治疗后1个月、3个月及6个月时检查并记录全口牙周临床指标。包括主要临床评价指标探诊深度(probing depth, PD);次要临床评价指标出血指数(bleeding index, BI)和探诊出血(bleeding on probing, BOP)。牙周探诊分别在牙的颊(唇)、舌面远中、中央、近中测量,每个牙记录6个位点的PD。在完成每个象限的颊部或舌部的探诊后,记录存在或不存在出血。所有检查均由同一名不知晓患者治疗策略的高年资牙周专科医师完成。

1.5 统计学分析

本研究统计学分析基于符合方案数据集进行

分析。使用Shapiro-Wilk检验和Q-Q绘图法评估数据的正态性。在基线,对满足正态性的计数资料(PD、PLI、BI和PD ≥ 5 mm位点占比)采用方差分析法进行组间差异分析,结果使用均值 ± 标准差表示。BOP位点阳性占比(BOP%)则采用Mann-Whitney U检验,结果使用中位数(四分位距)表示。随访时,采用两因素重复测量方差分析分析组间和组内差异。所有统计分析使用SPSS 22.0软件包进行分析,α = 0.05。

2 结果

2.1 基线资料

16例患者入组,受试者男女比例7:9,平均年龄(39.03 ± 8.26)岁,3例患者在3个月随访时脱落(脱落患者未纳入统计),13例患者完成了全部随访,对照侧356颗受试牙,2 136个位点;试验侧360颗受试牙,2 160个位点纳入研究分析。对照侧(SRP)PD均值(4.38 ± 0.72)mm,PD ≥ 5 mm位点占比44.87% ± 16.68%,BI均值3.45 ± 0.34,BOP% P_{50} (IQR)为93(18)。试验侧(SRP+aPDT)PD均值(4.26 ± 0.88)mm,PD ≥ 5 mm位点占比42.53% ± 19.29%,BI均值3.36 ± 0.36,BOP% P_{50} (IQR)为96(20),见表1。研究期间未出现不良事件。

表1 慢性牙周炎患者基线资料

Table 1 Baseline data of patients with chronic periodontitis

Group	Age/ years	Male/female	PLI	BI	BOP% [P_{50} (IQR)]	PD/mm	PD ≥ 5 mm
SRP	39.03 ± 8.26	7/9	3.72 ± 0.60	3.45 ± 0.34	93(18)	4.38 ± 0.72	44.87% ± 16.68%
SRP+aPDT	39.03 ± 8.26	7/9	3.54 ± 0.56	3.36 ± 0.36	96(20)	4.26 ± 0.88	42.53% ± 19.29%

SRP: scaling and root planing. aPDT: antibacterial photodynamic therapy. PLI: plaque index. BOP: bleeding on probing. BI: bleeding index. PD: probing depth

2.2 临床疗效比较

2.2.1 两侧治疗前后口腔卫生和牙周炎症状况比较 PLI、BI和BOP阳性位点占比两组基线均无显著差异。从基线水平到治疗后3个月和6个月,两组的平均PLI均有显著改善($P < 0.001$)。治疗后3个月,SRP+aPDT侧(试验侧)PLI的改善相较于SRP侧(对照侧)更明显,有显著差异($P < 0.001$)。这一差异维持到治疗后6个月($P = 0.002$)(表2)。

两组BI和BOP治疗后也有明显改善($P < 0.01$)。两组在各时间点BI均无统计学差异。但在治疗后3个月时SRP+aPDT侧BOP%明显低于SRP侧,有显著差异($P = 0.03$)(表3)。

表2 牙周基础治疗后1、3、6个月时两组PLI比较

Table 2 Comparisons of the PLI 1, 3 and 6 months after periodontal nonsurgical treatment

Group	Baseline	1 month	3 months	6 months
SRP	3.72 ± 0.60	2.72 ± 0.30 ^{##}	2.42 ± 0.20 ^{##}	2.62 ± 0.25 ^{##}
SRP+aPDT	3.54 ± 0.56	2.44 ± 0.16 ^{##}	2.04 ± 0.26 ^{##}	2.34 ± 0.24 ^{##}
F	1.615	3.760	18.05	12.456
P	0.217	0.065	< 0.001	0.002

Significant intragroup differences compared to baseline, ##, $P < 0.001$. SRP: scaling and root planing. aPDT: antibacterial photodynamic therapy. PLI: plaque index

表3 牙周基础治疗后1、3、6个月两组牙龈出血比较

Table 3 Comparisons of gingival bleeding 1, 3 and 6 months after periodontal nonsurgical treatment

Group	BI ($\bar{x} \pm s$)				BOP% [P_{50} (IQR)]			
	Baseline	1 month	3 months	6 months	Baseline	1 month	3 months	6 months
SRP	3.45 ± 0.34	2.76 ± 0.31 [#]	2.75 ± 0.26 [#]	2.76 ± 0.29 [#]	93 (18)	65 (47) [#]	56 (37) [#]	50 (23) ^{##}
SRP+aPDT	3.36 ± 0.36	2.74 ± 0.25 [#]	2.72 ± 0.22 [#]	2.60 ± 0.33 [#]	96 (20)	54 (46) [#]	42 (14) ^{##}	46 (22) ^{##}
<i>F</i>	0.212	0.047	0.057	1.474	0.241	2.01	6.308	0.88
<i>P</i>	0.650	0.83	0.814	0.239	0.631	0.178	0.030	0.37

Significant intragroup differences compared to baseline, [#] $P < 0.01$; ^{##} $P < 0.001$. SRP: scaling and root planing. aPDT: antibacterial photodynamic therapy. BI: bleeding index. BOP: bleeding on probing

2.2.2 两侧治疗前后PD水平 治疗1个月、3个月和6个月后,两组PD均值显著下降($P < 0.001$)。1个月随访时SRP侧PD下降到(2.82±0.37)mm,6个月时仍保持在(2.61 ± 0.38)mm;而SRP+aPDT侧1个月和6个月时的PD均值分别为(2.73 ± 0.47)mm和(2.57 ± 0.47)mm。SRP+aPDT侧和SRP侧显示出类似的探诊深度的减少,两组之间差异无统计学意义($P > 0.05$)(表4)。PD ≥ 5 mm位点占比改变趋势和PD均值一致,两组间差异无统计学意义(表5)。

表4 牙周基础治疗前后两组PD比较

Table 4 Comparisons of the PD before and after periodontal non-surgical treatment in the two groups mm, $\bar{x} \pm s$

Group	Baseline	1 month	3 months	6 months
SRP	4.38 ± 0.72	2.82 ± 0.37 ^{##}	2.70 ± 0.37 ^{##}	2.61 ± 0.38 ^{##}
SRP+aPDT	4.26 ± 0.88	2.73 ± 0.47 ^{##}	2.64 ± 0.44 ^{##}	2.57 ± 0.47 ^{##}
<i>F</i>	0.159	0.350	0.094	0.055
<i>P</i>	0.693	0.559	0.763	0.817

^{##}: significant intra-group differences compared to baseline, $P < 0.001$. SRP: scaling and root planing. aPDT: antibacterial photodynamic therapy. PD: probing depth

表5 牙周基础治疗后1、3、6个月两组PD ≥ 5 mm位点占比比较

Table 5 Comparisons of the ratio of sites with a PD ≥ 5 mm at 1, 3 and 6 months after periodontal nonsurgical treatment $\bar{x} \pm s$

Group	Baseline	1 month	3 months	6 months
SRP	44.87% ± 16.68%	13.07% ± 7.91% ^{##}	13.07% ± 7.91% ^{##}	9.64% ± 5.55% ^{##}
SRP+aPDT	42.53% ± 19.29%	12.47% ± 9.17% ^{##}	10.18% ± 6.11% ^{##}	9.45% ± 5.68% ^{##}
<i>F</i>	0.126	0.104	0.032	0.010
<i>P</i>	0.726	0.751	0.862	0.921

^{##}: significant intra-group differences compared to baseline, $P < 0.001$. SRP: scaling and root planing. aPDT: antibacterial photodynamic therapy. PD: probing depth

3 讨论

本研究旨在评估aPDT辅助SRP治疗慢性牙周炎的临床疗效。传统SRP虽然能显著改善牙周健康状况,但在彻底清除深牙周袋中病原体及防止其对邻近软组织的侵入和定植方面存在局限。研究指出,治疗后牙周病原菌的细胞内存留可能导致病原体在牙周袋内的重新定植,从而引发牙周炎的复发^[7-9]。尽管全身和局部抗生素治疗曾被认为是牙周炎的有效辅助治疗手段,但其潜在的抗药性和相关副作用限制了这些方法的广泛应用。而相比于全身抗生素的使用,aPDT无细胞毒性、可作为局部分子靶点短时间破坏细菌、真菌、病毒等复杂微生物结构^[10],不会产生细菌耐药性。aPDT对于抗菌素耐药和抗菌素敏感的菌群有相同的效

用,重复的光敏剂使用也不会导致选择性的耐药产生^[11]。Zago等^[12]近期的一项研究报道指出,对甲硝唑耐药的临床龈下菌斑对亚甲基蓝、二氢卟吩e6和姜黄素介导的aPDT敏感。光敏剂分子的结构特点使其更易聚集在生长旺盛的细胞中,微生物由于繁殖迅速,比正常体细胞对光敏剂亲和性更强。因此,aPDT在对抗口腔感染方面具有潜力。

研究表明,红色激光结合适当的光敏剂(如甲苯胺蓝、酞菁、二氢卟吩等)对多种口腔病原体具有杀灭作用^[13],aPDT的辅助使用能使牙周临床指标的改善效果更加显著^[4,14-15]。Al-Momani等^[16]的研究进一步显示,对于伴2型糖尿病Ⅲ期C级牙周炎患者,治疗后3个月时无论是血糖控制良好或是控制不良的患者,相较于单独SRP组,吡啶菁绿介

导的 aPDT 辅助治疗组 PD、BOP 等临床参数改善更明显。Cláudio 等^[17]的研究也表明,对非代偿期糖尿病伴牙周炎患者进行多个疗程的 aPDT 治疗,可有显著的临床获益。Schär 等^[18]也指出 aPDT 对于控制残存牙周袋的炎症和出血有显著意义。同时,也有很多研究并没有发现 aPDT 的额外临床获益^[19-20]。Tabenski 等^[21]的研究认为与单独使用 SRP 相比,辅助 aPDT 或米诺环素微球对深牙周袋都没有显著的额外临床指标改善。

本研究采用自身对照分口设计的随机临床试验以消除平行对照试验中的个体差异带来的偏倚,试验组接受两次 aPDT 治疗(SRP 同期及 1 个月随访时)。研究结果显示 aPDT 联合治疗在牙周探诊深度上可以获得和常规 SRP 相似的改善。而在 BOP% 的改善上 3 个月时明显优于 SRP 组 ($P < 0.05$),提示 aPDT 联合治疗有助于早期改善牙龈炎症。这与 Braun 等^[22]的研究结果一致。Coelho 等^[11]针对 11 例患者 38 颗磨牙的分口设计研究也显示 aPDT 联合治疗侧相较于 SRP 侧,治疗后 3 个月时,BOP 和 PD 的减少更明显。Brinar 等^[23]也指出 aPDT (1 mg/mL 吡啶菁绿,810 nm,250 mW,60 s)辅助 SRP 与单独 SRP 相比,对于伴 2 型糖尿病牙周炎患者的 BOP(治疗后 90 d)也有明显改善。虽然欧洲牙周病学会牙周炎治疗 S3 级临床指南^[24]在慢性牙周炎基础治疗中不推荐龈下刮治联合使用 aPDT,但随后 Skalerič 等^[25]比较 aPDT 和抗生素治疗作为常规非手术治疗的辅助治疗对侵袭性牙周炎患者的研究显示,aPDT 在治疗后 3 个月提供了和抗生素类似的显著临床改善,并在治疗后 12 个月保持下降。Costa 等^[26]最近使用吡啶菁绿介导的 aPDT 辅助治疗维护期残余牙周深袋(PD ≥ 5 mm),相较于单纯 SRP 可显著降低 BOP 阳性位点以及牙龈卟啉单胞菌 *P.g* 和伴放线聚集杆菌 *A.a* 水平。

综上,本研究结果提示 aPDT 联合治疗相较于单纯龈下刮治,尽管在牙周探诊深度的改善上并未表现出明显获益,但在探诊出血即控制牙周炎症水平上有一定优势。aPDT 作为龈下刮治和根面平整术的辅助治疗手段,可以在早期更好地改善牙龈出血,控制牙周炎症。但如何在牙周基础治疗中使用 aPDT,以提高牙周基础治疗效果,改善患者的牙周生态,仍需进一步探讨。

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