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盐酸米诺环素软膏辅助龈下刮治术及根面平整术对慢性牙周炎患者龈下牙周致病菌和龈沟液炎性因子的影响*

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摘要 目的:探讨盐酸米诺环素软膏辅助龈下刮治术及根面平整术(FM-SRP)对慢性牙周炎(CP)患者龈下牙周致病菌和龈沟液炎性因子的影响。**方法:**选择2015年10月到2019年10月期间我院收治的82例CP患者,根据随机数字表法分为对照组(n=41)和观察组(n=41),对照组给予FM-SRP,观察组在对照组基础上联合盐酸米诺环素软膏辅助治疗,比较两组疗效、牙周指标、龈下牙周致病菌和龈沟液炎性因子情况,统计两组不良反应情况。**结果:**与对照组总有效率70.73%(29/41)相比,观察组治疗后的总有效率90.24%(37/41)更高($P<0.05$)。治疗后,两组龈沟出血指数(SBI)、附着水平(AL)、菌斑指数(PLI)、牙周袋深度(PD)均下降,且观察组低于对照组($P<0.05$)。治疗后,两组转化生长因子- β (TGF- β)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)均下降,且观察组低于对照组($P<0.05$)。对比两组不良反应无差异($P>0.05$)。治疗后,两组伴防线杆菌、牙龈卟啉单胞菌比例均下降,且观察组低于对照组($P<0.05$)。**结论:**盐酸米诺环素软膏辅助FM-SRP治疗CP患者,可有效消除致病菌,缓解炎症反应,恢复牙周生态平衡,且不增加不良反应发生率,疗效确切。

关键词: 盐酸米诺环素软膏; 龈下刮治术; 根面平整术; 慢性牙周炎; 牙周致病菌; 炎性因子

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Effects of Minocycline Hydrochloride Ointment Assisted Subgingival Scaling and Root Planing on Subgingival Periodontal Pathogens and Gingival Crevicular Fluid Inflammatory Factors in Patients with Chronic Periodontitis*

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ABSTRACT Objective: To investigate the effects of minocycline hydrochloride ointment assisted subgingival scaling and root planing (FM-SRP) on subgingival periodontal pathogens and gingival crevicular fluid inflammatory factors in patients with chronic periodontitis (CP). **Methods:** A total of 82 patients with CP who were admitted to our hospital from October 2015 to October 2019 were selected, they were divided into control group (n=41) and observation group (n=41) according to random number table method. The control group was given FM-SRP, and the observation group was treated with minocycline hydrochloride ointment on the basis of the control group. The efficacy, periodontal indexes, subgingival periodontal pathogens and gingival crevicular fluid inflammatory factors were compared between the two groups, the adverse reactions of the two groups were counted. **Results:** Compared with the total effective rate of 70.73% (29/41) in the control group, the total effective rate of 90.24% (37/41) in the observation group after treatment was higher ($P<0.05$). After treatment, The sulcus bleeding index (SBI), attachment level (AL), plaque index (PLI) and periodontal pocket depth (PD) of the two groups decreased, and the observation group was lower than the control group ($P<0.05$). After treatment, the transforming growth factor- β (TGF- β), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) levels of the two groups decreased, and the observation group was lower than the control group ($P<0.05$). There was no difference in adverse reactions between the two groups ($P>0.05$). After treatment, the proportion of *Bacillus parahaemolyticus* and *Porphyromonas gingivalis* decreased in both groups, and the observation group was lower than the control group ($P<0.05$). **Conclusion:** Minocycline hydrochloride ointment assisted FM-SRP in the treatment of patients with CP can effectively eliminate the pathogenic bacteria, alleviate the inflammatory reaction, restore the periodontal ecological balance, and does not increase the incidence of adverse reactions, with definite curative effect.

Key words: Minocycline hydrochloride ointment; Subgingival scaling; Root planing; Chronic periodontitis; Periodontal pathogens; Inflammatory factors

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前言

慢性牙周炎(CP)为口腔科常见的一种感染性疾病,该疾病可发生于任何年龄,但多见于成年人,且35岁以后的患病率明显升高^[1,2]。CP的主要症状表现为牙龈出血、牙龈炎症、牙周袋形成以及牙槽骨吸收等,影响了患者的口腔健康、咀嚼、美观及心理健康,降低生活质量^[3,4]。目前临床治疗CP的主要方式为龈下刮治术及根面平整术(FM-SRP),并服用抗生素辅助治疗。上述疗法虽能消除龈下病原菌,但术后会引起感染,从而导致炎症的发生,这对患者往后的恢复是不利的,且抗生素口服的方式无法达到最佳的牙龈局部药物浓度,降低治疗效果^[5,6]。盐酸米诺环素软膏是一种有着抗菌高效、易渗透优点的抗生素,既往常用于牙周疾病的治疗中^[7,8]。本研究通过探讨盐酸米诺环素软膏辅助FM-SRP治疗CP患者的应用情况,分析上述治疗对患者龈下牙周致病菌和龈沟液炎症因子的影响,整理如下。

1 资料与方法

1.1 临床资料

选择2015年10月到2019年10月期间我院收治的82例CP患者,本研究经医院伦理委员会审核批准。纳入标准:(1)诊断标准参考《牙周病学》^[9];(2)入组前6个月内未接受过任何牙周治疗;(3)签订知情同意书者;(4)口内可行牙周评价牙 ≥ 20 颗,磨牙数 ≥ 4 颗。排除标准:(1)妊娠或哺乳期妇女;(2)伴有其他慢性或系统炎症患者;(3)伴有严重内分泌系统疾病、心脑血管疾病者;(4)治疗期间不愿戒酒、戒烟者;(5)肝肾功能有严重障碍者;(6)对本研究用药有禁忌症者;(7)正畸或口腔黏膜病患者。根据随机数字表法将患者分为对照组($n=41$)和观察组($n=41$),其中对照组男、女分别为24例、17例,年龄44~68岁,平均 (49.01 ± 3.16) 岁;病程2~7年,平均 (4.42 ± 0.71) 年。观察组男、女分别为25例、16例,年龄45~66岁,平均 (48.86 ± 3.27) 岁;病程3~7年,平均 (4.24 ± 0.73) 年。对比两组临床资料无差异($P>0.05$),均衡可比。

1.2 方法

两组患者入院后进行全口曲面断层片检查,口服伐昔洛韦[四川汇诚药业有限公司,国药准字H20093538,规格:0.3 g],500 mg/d,2次/d,连用1周。用药结束48 h后给予手术治疗,所有手术操作均由同一组医师完成操作,在局部麻醉下进行

FM-SRP,术后采用3%的双氧水冲洗患者牙周袋。术后禁食辛辣厚味、过冷过热等刺激性食物,合理应用牙间隙刷,常规服用抗生素、抗炎药物治疗。在上述方法上,观察组联合盐酸米诺环素软膏(规格:0.5 g, Sunstar INC.,注册证号:H20150106)治疗,龈下刮治后,用软膏注满患部牙周袋内,1次/周,连用4周。

1.3 观察指标

(1)观察两组治疗后的总有效率。总有效率=显效率+有效率^[10]。显效:牙龈指数减小 $\geq 1/2$,患者牙周袋深度(PD)减小 ≥ 2 mm,临床症状消失。有效:症状减轻,有好转,PD减小 ≥ 1 mm并小于2 mm。无效:症状没有减轻甚至恶化。(2)记录两组治疗前后的牙周指标情况,包括龈沟出血指数(SBI)、附着水平(AL)、菌斑指数(PLI)、PD^[11]。其中SBI根据病情程度进行评估,以数字0~5表示病症程度,0和1分别代表完全和基本健康,2、3、4和5依次代表轻微、明显、较重和重度龈炎,数字越大病情越重。AL为探针深度减去釉牙骨质界至龈缘的距离。PLI以数字0~3分别表示近龈缘处牙面无菌斑;近龈缘处牙面有薄菌斑,以肉眼观察不可见,探针划过可见;龈缘区或牙邻面肉眼可见中等量菌斑覆盖,但不超过2/3;菌斑覆盖牙面2/3或以上。PD为牙周探针测量的牙龈与牙齿之间的龈沟深度。(3)记录两组治疗期间不良反应情况。(4)于治疗前后于舌侧近中、颊侧近中、颊侧远中、舌侧远中四处以滤纸条吸取龈沟液,若吸潮纸尖表面有污染物,则重新提取龈沟液,若没有则置于EP试剂管中,加PBS缓冲液,经3300 r/min离心12 min,离心半径14 cm,取上清液保存待测。采用酶联免疫吸附法检测转化生长因子- β (TGF- β)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α),试剂盒均购自北京键平九星生物科技有限公司,按试剂盒说明书严格操作。(5)治疗前后,收集并测定两组口腔两个象限内的PD >5 mm处的斑菌。

1.4 统计学方法

数据采用SPSS26.0软件分析,计数资料以例数及率表示,行 χ^2 检验,计量资料用 $(\bar{x} \pm s)$ 表示,行t检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 总有效率

与对照组总有效率70.73%(29/41)对比,观察组治疗后的总有效率90.24%(37/41)更高($P<0.05$),见表1。

表1 两组总有效率比较[例(%)]

Table 1 Comparison of total effective rate between two groups [n(%)]

Groups	Remarkable effect	Effective	Invalid	Total effective rate
Control group($n=41$)	11(26.83)	18(43.90)	12(29.27)	29(70.73)
Observation grou($n=41$)	16(39.02)	21(51.22)	4(9.76)	37(90.24)
χ^2				6.733
P				0.009

2.2 牙周指标

治疗前对比两组牙周指标无差异($P>0.05$),治疗后两组SBI、AL、PLI、PD比治疗前更低,且观察组比对照组低($P<0.05$),见表2。

2.3 龈沟液炎症因子

治疗前对比两组炎症因子无差异($P>0.05$),治疗后TGF- β 、IL-6、TNF- α 比治疗前更低,且观察组较对照组更低($P<0.05$),见表3。

表 2 两组牙周指标情况比较($\bar{x} \pm s$)Table 2 Comparison of periodontal indexes between the two groups($\bar{x} \pm s$)

Groups	SBI		AL (mm)		PLI		PD (mm)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=41)	3.19 $\pm$ 0.27	1.52 $\pm$ 0.23*	4.39 $\pm$ 0.47	2.84 $\pm$ 0.31*	2.43 $\pm$ 0.27	1.51 $\pm$ 0.24*	4.27 $\pm$ 0.32	2.89 $\pm$ 0.29*
Observation group (n=41)	3.13 $\pm$ 0.32	0.93 $\pm$ 0.17*	4.35 $\pm$ 0.38	1.33 $\pm$ 0.38*	2.48 $\pm$ 0.35	0.93 $\pm$ 0.16*	4.33 $\pm$ 0.36	1.73 $\pm$ 0.23*
t	0.918	13.209	0.424	19.716	0.724	12.875	0.798	20.067
P	0.362	0.000	0.673	0.000	0.471	0.000	0.427	0.000

Note: compared with before treatment, * $P < 0.05$.表 3 两组龈沟液炎症因子指标比较($\bar{x} \pm s$, pg/mL)Table 3 Comparison of gingival crevicular fluid inflammatory factors indexes between the two groups($\bar{x} \pm s$, pg/mL)

Groups	TGF- β		IL-6		TNF- α	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=41)	24.78 $\pm$ 2.37	16.42 $\pm$ 2.33*	23.56 $\pm$ 2.39	14.36 $\pm$ 2.32*	24.88 $\pm$ 3.27	17.64 $\pm$ 3.29*
Observation group (n=41)	24.52 $\pm$ 3.48	12.16 $\pm$ 2.41*	22.93 $\pm$ 2.35	8.39 $\pm$ 1.35*	24.94 $\pm$ 3.39	11.87 $\pm$ 2.18*
t	0.395	8.137	1.204	14.241	0.082	9.361
P	0.694	0.000	0.232	0.000	0.935	0.000

Note: compared with before treatment, * $P < 0.05$.

2.4 龈下牙周致病菌

两组治疗前伴防线杆菌、牙龈卟啉单胞菌比例对比差异未见统计学意义($P > 0.05$),治疗后两组伴防线杆菌、牙龈卟啉单胞菌比例比治疗前更低,且观察组较对照组更低($P < 0.05$),见

表 4。

2.5 不良反应

对比两组不良反应无差异($P > 0.05$),见表 5。

表 4 两组龈下牙周致病菌比较($\bar{x} \pm s$)Table 4 Comparison of subgingival periodontal pathogens between the two groups($\bar{x} \pm s$)

Groups	Bacillus parahaemolyticus		Porphyromonas gingivalis	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=41)	0.026 $\pm$ 0.002	0.021 $\pm$ 0.002*	0.48 $\pm$ 0.07	0.36 $\pm$ 0.09*
Observation group (n=41)	0.026 $\pm$ 0.003	0.015 $\pm$ 0.001*	0.47 $\pm$ 0.09	0.22 $\pm$ 0.07*
t	0.000	17.181	0.915	7.862
P	1.000	0.000	0.363	0.000

Note: compared with before treatment, * $P < 0.05$.

表 5 两组不良反应发生率比较 [例(%)]

Table 5 Comparison of the incidence of adverse reactions between the two groups [n(%)]

Groups	Dizzy	Nausea	Itch	Total incidence rate
Control group (n=41)	2(4.88)	1(2.44)	1(2.44)	4(9.76)
Observation group (n=41)	3(7.32)	2(4.88)	1(2.44)	6(14.63)
χ^2				0.456
P				0.500

3 讨论

经济的发展,改变了人们的生活与饮食习惯,生活节奏的

加快也带动了人们不良生活习惯的养成,如不按时刷牙、饮食不健康、不注重口腔清洁等,这些容易造成牙齿牙龈损伤,进而引起口腔溃疡、牙龈出血等口腔疾病^[12-14]。CP 作为由细菌感染

引起的口腔科常见疾病,据以往数据报道显示^[15],全球约有75%的成年人至少有过CP史,CP已成为成年人牙齿缺失的主要原因之一。CP的发病机制复杂,以牙菌斑中病原微生物为始动因子,主要是由于厌氧菌以菌斑的形式黏附于牙体表面,加上宿主自身身体的易感性,导致附着于牙体表面的菌斑的菌体在发生裂解后会释放出大量有强致炎作用的毒素,对牙周支持组织部位造成一系列的破坏,最终引起牙齿松动或失牙^[16-18]。牙周基础治疗(包括口腔卫生指导、龈下刮治、根面平整等)作为CP的主要治疗手段,多数情况下可将患者龈上龈下的菌斑清除干净,同时还可破坏患者牙周细菌的生存环境,为牙周组织的再生创造有利条件^[19,20]。但是上述疗法容易受到个体差异性的影响,因为患者的牙根、牙周袋形态不尽相同,牙周环境也存在差异,常规基础治疗并不能控制所有患者牙周袋中的细菌感染,易导致病情反复,因此通常需要配合药物进行治疗。

盐酸米诺环素软膏具有广谱抗菌、作用时间长、活性强的特点,可有效抑制厌氧菌的繁殖增生^[21]。同时该软膏还能极大的降低机体胶原酶的活性,从而有效降低牙周组织的损坏程度,降低骨吸收,刺激患者牙周组织的再生,增强牙周细胞的附着能力,并促进其更快生长,改善患者症状^[22]。与口服抗生素不同的是,盐酸米诺环素软膏可直接注入到患病部位并发挥作用,从而使病变组织周围药物浓度维持在一定水平,起到长久高效的杀菌效果^[23]。本研究结果还显示,盐酸米诺环素软膏辅助FM-SRP治疗CP患者,能有效促进牙周相关指标的改善,进而提高治疗效果。既往研究结果表明^[24,25],随着CP的不断发展,患者局部患病部位的炎性因子可发生转移现象,例如龈沟液部位的TGF- β 、IL-6、TNF- α 等炎性因子可穿透溃烂上皮组织,从而转移到人体内循环中,导致局部炎症反应进展为全身炎症反应。其中IL-6可直接损害牙周支持组织,TNF- α 是一种细胞因子,可对细胞产生刺激,在人体淋巴细胞和巨噬细胞生成,TGF- β 是免疫稳态和免疫耐受的重要促进因子,可促进炎症性疾病的发生。本研究中,盐酸米诺环素软膏辅助FM-SRP治疗可缓解CP患者机体炎症反应。可能与盐酸米诺环素软膏本身具备较强的抗菌、抗炎作用,从而纠正机体免疫紊乱状态有关。以往报道表明^[26,27],在预防牙周病方面,维持好伴防线杆菌和牙龈卟啉单胞菌的菌落平衡很重要,上述菌群的大量繁殖可破坏龈下牙周环境,引发菌群失衡,进而引起CP的产生。因此,观察伴防线杆菌、牙龈卟啉单胞菌的比例有助于判断CP的疾病进程及治疗效果。本研究中两组患者牙周致病菌比例均下降,且盐酸米诺环素软膏辅助FM-SRP治疗的下降更明显,提示联合方案抗菌效果显著。盐酸米诺环素软膏可有效抑制菌斑微生物,特别是在抑制牙周致病菌上具有显著的功效,并能通过抑制牙周结缔和骨组织的破坏,达到降低骨吸收的效果,有利于牙周组织细胞在根面上的增殖和再附着,从而消除致病菌的菌斑附着^[28-30]。此外,盐酸米诺环素软膏的安全性一直存在着一定的争议,而观察两组安全性可知,CP患者在FM-SRP治疗后联合盐酸米诺环素软膏,不会增加不良反应发生率,安全有效。

综上所述,盐酸米诺环素软膏辅助FM-SRP治疗CP患者,可有效消除致病菌,恢复牙周生态平衡,且不增加不良反应

发生率,疗效确切,其内在机制可能与降低TGF- β 、IL-6、TNF- α 等炎性因子水平有关。

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