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甲硝唑药膜联合盐酸米诺环素软膏治疗牙周病的临床疗效分析

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摘要 目的:研究甲硝唑药膜联合盐酸米诺环素软膏治疗牙周病的临床疗效。**方法:**选择 2014 年 1 月~2016 年 1 月在我院进行治疗的牙周病患者 80 例,随机分为两组。观察组采用甲硝唑药膜联合盐酸米诺环素软膏治疗,对照组采用甲硝唑药膜治疗。观察并比较两组的疗效,牙周附着指数、牙菌斑指数、牙龈指数、牙齿松动度和白介素 -6、白介素 -8 和肿瘤坏死因子的水平。**结果:**治疗 4 周后,观察组的治疗有效率为 95.0%,明显高于对照组的 90.0% ($P<0.05$);治疗后两组的牙周附着指数、牙菌斑指数、牙龈指数和牙齿松动度均较治疗前明显降低($P<0.05$),且观察组的降低程度明显优于对照组($P<0.05$);治疗后两组的肿瘤坏死因子、白介素 -6 和白介素 -8 均较治疗前明显降低($P<0.05$),且观察组的降低程度明显优于对照组($P<0.05$);两组间丘疹、恶心、胃肠道反应和失眠的发生情况相比无明显差异($P>0.05$);观察组的复发率为 2.5%,明显低于对照组的 7.5% ($P<0.05$)。**结论:**甲硝唑药膜联合盐酸米诺环素软膏能增强对牙周病各种致病菌的抑制作用,提高临床疗效,改善牙周状况和炎症状态,不良反应少,且复发率低,值得推广应用。

关键词:甲硝唑药膜;盐酸米诺环素软膏;牙周病

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Clinical Effect of Metronidazole Membrane combined with Minocycline Ointment for Periodontal Disease

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ABSTRACT Objective: To investigate the clinical effect of metronidazole membrane combined with minocycline ointment on periodontal disease. **Methods:** 80 cases of patients with periodontal disease in our hospital from January 2014 to January 2016 were select and divided into observation group and control group. The patients in the observation group were treated with metronidazole membrane combined with minocycline ointment, and the patients in the control group were adopted metronidazole membrane. The curative effect, periodontal attachment index, plaque index, gingival index, tooth mobility degree and the levels of serum IL-2, IL-6, IL-8 and TNF were compared between the two groups. **Results:** After 4 weeks, The curative effect of the observation group (95.0%) was significantly higher than that of the control group (90.0%) ($P<0.05$); the periodontal attachment index, plaque index, gingival index and tooth mobility degree and the levels of serum IL-2, IL-6, IL-8 and TNF in two groups were all were significantly decreased ($P<0.05$), and the reduce degree of observation group was more obviously than that of the control group ($P<0.05$); no difference was found between the two groups as to pimples, nausea and gastrointestinal reaction and insomnia ($P>0.05$); the recurrence rate of the observation group (2.5%) was significantly lower than that of the control group (7.5%). **Conclusions:** Metronidazole membrane combined with minocycline ointment can enhance inhibition of periodontal pathogens, and improve the clinical effect, the periodontal condition and state of inflammation, and has less adverse reactions, low recurrence rate, worthy of application.

Key words: Metronidazole membrane; Minocycline ointment; Periodontal disease

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前言

牙周病是是口腔常见疾病之一,临床症状主要包括牙齦出

血、牙齦炎症、牙齿松动和肿胀等,具有较高的发病率和复发率,可伴有溢脓、疼痛、口臭等并发症,影响正常咀嚼及发音^[1-3]。米诺环素在四环素类中抗菌作用最强,链球菌、金黄色葡萄球菌、大肠杆菌虽对四环素耐药,但对米诺环素敏感性仍较强^[4];甲硝唑可清除口腔内的革兰氏阴性厌氧菌^[5]。二者已被广泛用于牙周病的治疗中,目前临床上有关两种药物联合使用的报道,但是对于患者用药后体内炎症因子的观测相关研究较少

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见,因此本文研究了甲硝唑药膜联合盐酸米诺环素软膏在牙周病治疗中的应用效果,并观察患者用药前后体内炎症因子水平的变化情况。现进行如下报道。

1 资料与方法

1.1 一般资料

80例牙周病患者来自我院2014年1月至2016年1月,共82颗患牙,随机分为两组。治疗组40例(40颗),男22例,女18例;年龄23~64岁,平均(35.12±8.35)岁;其中前磨牙11颗,前牙13颗,磨牙16颗;牙龈炎7颗,单纯性牙周炎23颗,牙周脓肿10颗。对照组40例(40颗),男21例,女19例;年龄22~63岁,平均(36.32±7.38)岁;其中前磨牙10颗,前牙12颗,磨牙18颗;牙龈炎6颗,单纯性牙周炎25颗,牙周脓肿9颗。本研究获得我院伦理委员会批准,所有入组患者均签署知情同意书。两组基线资料具有可比性($P<0.05$)。

1.2 治疗方法

所有患者在治疗前均清洁患部,用双氧水和氯化钠溶液反复冲洗口腔病变部位。对照组:往病变部位牙周袋内注射入盐酸米诺环素(日本SUNSTAR株式会社药厂生产,批号:1509041,规格0.5g/支),直到注满;观察组:在对照组的基础上,按照牙周袋的深度剪下大小适合的甲硝唑药膜(康美药业股份有限公司生产,批号:080113),放在牙周袋底部。两组均每周给药1次,连续治疗4周。

1.3 观察指标

观察并比较两组的疗效,牙周附着指数、牙菌斑指数、牙龈指数和牙齿松动度。采用酶联免疫法检测白介素-6、白介素-8和肿瘤坏死因子的水平。观察治疗期间两组患者的不良反应发生情况,并在治疗后半年通过每月定期电话随访获得患者复发情况。不良反应包括:丘疹、恶心、胃肠道反应和失眠等;电话随访询问患者有无牙龈出血、牙龈炎症、牙齿松动和肿胀等症状再次出现,如其中任何一种症状出现即为复发。

疗效判断标准^[6]:①治愈:患者的牙龈基本恢复正常,各种症状均消失或转阴;②显效:患者的疼痛症状和牙龈出血得到明显改善,牙周袋深度减少 >2 mm,牙龈指数降低 $>40\%$;③有效:患者的疼痛症状和牙龈出血有所改善;④无效:患者的各种症状均无改善。

1.4 统计学分析

采用SPSS15.00软件,计量资料以 $\bar{x}\pm s$ 表示,组间比较用t检验,组内比较用方差分析,组间率比较用 χ^2 检验,以 $P<0.05$ 表明差异有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组有效率(95.0%)明显高于对照组(90.0%)($P<0.05$),见表1。

表1 两组临床疗效比较[例(%)]

Table 1 Comparison of the curative effect between two groups [n(%)]

Groups	n	Clinical cure	Excellence	Improvement	Failure	Effective rate
Observation group	40	16(40.0)	13(32.5)	9(22.5)	2(5.0)	38(95.0) *
Control group	40	11(27.5)	12(30.0)	13(32.5)	4(10.0)	36(90.0)

Note: compared with the control group, * $P<0.05$.

2.2 两组牙周病治疗情况的比较

治疗后两组的牙周附着指数、牙菌斑指数、牙龈指数和牙齿松动度均较治疗前降低($P<0.05$),且治疗后,观察组的牙周附

着指数、牙菌斑指数、牙龈指数和牙齿松动度均明显优于对照组($P<0.05$),见表2。

表2 两组牙周病治疗情况的比较($\bar{x}\pm s$)

Table2 Comparison of the periodontal therapy between two groups($\bar{x}\pm s$)

Groups		Periodontal attachment index(mm),	Plaque index	Gingival index	Tooth mobility degree (mm)
Observation group	Before treatment	8.43± 1.12	1.85± 0.36	2.82± 0.24	1.79± 0.32
	After treatment	5.65± 0.43**	0.46± 0.21**	0.65± 0.13**	0.32± 0.14**
Control group	Before treatment	8.52± 1.25	1.79± 0.42	2.86± 0.15	1.73± 0.41
	After treatment	7.62± 0.56 [#]	0.81± 0.26 [#]	1.02± 0.21 [#]	0.82± 0.15 [#]

Note: compared with the control group, * $P<0.05$; compared with before treatment, [#] $P<0.05$.

2.3 两组炎症因子水平的比较

与治疗前比较,治疗后两组的肿瘤坏死因子、白介素-6和白介素-8均较明显降低($P<0.05$),且治疗结束后观察组的各类炎症因子水平均明显优于对照组($P<0.05$),见表3。

2.4 两组不良反应和复发情况的比较

两组间丘疹、恶心、胃肠道反应和失眠的发生情况相比无明显差异($P>0.05$);观察组的复发率为2.5%,明显高于对照组的7.5%($P<0.05$),见表4。

表 3 两组炎症因子水平的比较($\bar{x} \pm s$)Table 3 Comparison of the inflammatory factor levels between two groups($\bar{x} \pm s$)

Groups		Tumor necrosis factor(TNF) (ng/L)	Interleukin-6(ng/L)	Interleukin-8(μ g/L)
Observation group	Before treatment	7.15 $\pm$ 1.23	71.58 $\pm$ 13.16	12.15 $\pm$ 3.12
	After treatment	4.12 $\pm$ 2.03 ^{*#}	26.38 $\pm$ 5.27 ^{*#}	5.42 $\pm$ 1.23 ^{*#}
Control group	Before treatment	7.26 $\pm$ 2.25	72.03 $\pm$ 12.15	13.02 $\pm$ 2.58
	After treatment	6.02 $\pm$ 2.34 [#]	39.26 $\pm$ 6.32 [#]	8.62 $\pm$ 1.54 [#]

Note: compared with the control group, *P<0.05; compared with before treatment, #P<0.05.

表 4 两组不良反应和复发情况的比较[例(%)]

Table 4 Comparison of adverse reaction rate and recurrence rate between two groups [n(%)]

Groups	n	Papule	Nausea	Gastrointestinal reaction	Insomnia	Adverse reaction rate	Recurrence rate
Observation group	40	0(0.0)	2(5.0)	1(2.5)	1(2.5)	4(10.0)	1(2.5) *
Control group	40	1(2.5)	2(5.0)	1(2.5)	1(2.5)	5(12.5)	3(7.5)

Note: compared with the control group, *P<0.05.

3 讨论

随着人们生活水平的不断提高,人们越来越重视并关注口腔卫生。牙周病是微生物引起的感染性疾病,属于感染性、非特异性、慢性疾病,是临床多发病和常见病,病变部位包括牙槽骨、牙齿支持组织、牙周韧带、牙龈和牙骨质等,严重危害患者的口腔健康和正常生活^[7-9]。据统计,我国牙周病的发病率在儿童和青少年中占 90%,而在成年人中高达 97%^[10]。如治疗效果不佳或未能给予及时有效的治疗,最终会引起牙齿松动甚至脱落。传统的治疗方案包括拔掉患牙和机械刮治,但会损伤牙根,加重疼痛程度,且不良反应多、复发率高,患者的依从性较低^[11]。

目前临床常用甲硝唑、盐酸米诺环素和碘甘油等药物治疗牙周病^[12,13]。甲硝唑能通过抑制 DNA 合成并进一步阻断 DNA 的转录,最终引起细菌死亡,主要作用于革兰氏阴性厌氧菌,而牙周病口腔内存在着大量牙龈单胞菌、产黑色素菌、普氏菌等厌氧菌,并能改善牙龈出血和肿痛,有效巩固牙齿^[14,15]。盐酸米诺环素作为一种广谱抗菌素,对牙周袋内多种致病菌有较好效果,并可有效促进牙周组织生成,稳固智齿^[16-18]。根据剂型不同,可分别用于局部治疗及全身治疗,由于局部用药易产生耐药菌株且药物浓度较低,全身用药毒副作用大,本研究采用米诺环素软膏,能在牙周袋内形成一层膜,缓慢而有控制地释放其药效成分,发挥持续抑制或灭菌的作用。

廖雪峰^[19]等的研究结果显示,甲硝唑药膜联合盐酸米诺环素软膏治疗牙周病的有效率要明显优于单用盐酸米诺环素软膏(95.7% vs 85.5%)。本文研究了甲硝唑药膜联合盐酸米诺环素软膏治疗牙周病的疗效,发现,观察组的有效率为 95.0%,明显高于对照组的 90.0%(P<0.05),同样表明了联合用药能提高对牙周病的治疗有效率;而本研究中单用盐酸米诺环素软膏的对照组的有效率要略高于相关参考文献^[19,20]的研究结果,可能原因为样本差异或牙周基础清洁和用药技术的差异治疗后两组的牙周附着指数、牙菌斑指数、牙龈指数和牙齿松动度均明显低于治疗前(P<0.05),且治疗后的各指标水平明显优于对照

组(P<0.05),表明联合用药能使病变牙周组织局部药物浓度提高,明显改善牙周病的相关病症。Arun 等^[21]发现,致病菌能提高牙周局部炎症因子水平,增强炎症反应,进而损伤牙周组织。肿瘤坏死因子、白介素 -6 和白介素 -8 能有效反映机体的炎症反应,当机体出现炎症时,其水平会有所升高^[22]。治疗后两组的肿瘤坏死因子、白介素 -6 和白介素 -8 均明显低于治疗前(P<0.05),且治疗后观察组的各炎症因子水平均明显优于对照组(P<0.05),表明联合用药治疗能改善炎症状态;两组间丘疹、恶心、胃肠道反应和失眠的发生情况相比无明显差异(P>0.05);表明联合用药不会增加不良反应,安全性较高,本研究中,观察组的复发率为 2.5%,明显低于对照组的 7.5%(P<0.05),表明与单独应用甲硝唑药膜相比,甲硝唑药膜联合应用盐酸米诺环素软膏能明显降低牙周病的复发率。综上所述,甲硝唑药膜联合盐酸米诺环素软膏能增强对牙周病各种致病菌的抑制作用,提高临床疗效,改善牙周状况和炎症状态,不良反应少,且复发率低,值得推广应用。

参考文献(References)

- [1] Fine D H, Cohen D W, Bimstein E, et al. Periodontitis: A Ninety-Year History: The Legacy of Professor Bernhard Gottlieb [J]. Journal of Periodontology, 2014, 86(1): 1-10
- [2] Lopes J R, Fernandes M M, Paiva L A S D, et al. Age estimation by teeth periodontitis and transparency: Accuracy of Lamendin's method on a Brazilian sample[J]. Brazilian Journal of Oral Sciences, 2014, 13 (1): 17-21
- [3] Fine D H, Cohen D W, Bimstein E, et al. Commentary: A Ninety-Year History of Periodontitis: The Legacy of Professor Bernhard Gottlieb [J]. Journal of periodontology, 2015, 86(1): 1-6
- [4] 夏丽文, 李大维, 姚丽娜. HPLC 法测定盐酸米诺环素缓释微丸胶囊中的米诺环素和有关物质[J]. 药物评价研究, 2012, 35(2): 117-119
- [5] 胡建立, 王寅丽. 甲硝唑治疗牙周病的临床观察[J]. 中国药房, 2014 (16): 1469-1470

- Hu Jian-li, Wang Yin-li. Clinical observation of metronidazole in the treatment of periodontal disease[J]. China Pharmacy, 2014(16):1469-1470
- [6] 彭源. 奥美拉唑、阿莫西林联合甲硝唑治疗牙周病的临床疗效观察[J]. 中国医药指南, 2012, 10(15): 517-518
- Peng Yuan. Clinical effect of omeprazole, amoxicillin combined with metronidazole on periodontal disease [J]. Guide of China Medicine, 2012, 10(15): 517-518
- [7] Schmitt A, Saliba Serre B, Tremblay M, et al. An evaluation of statistical methods for the determination of age of death using dental root translucency and periodontosis [J]. Journal of forensic sciences, 2010, 55(3): 590-596
- [8] Lopes J R, Queiroz S B B S, Fernandes M M, et al. Age estimation by teeth periodontosis and transparency: accuracy of Lamendin's method on a Brazilian sample[J]. Brazilian Journal of Oral Sciences, 2014, 13 (1): 17-21
- [9] Zorina O A, Kulakov A A, Rebrikov D V. Quantitative detection of periodontopatogenicmicroflora in periodontosis and healthy control [J]. Stomatologiia, 2010, 90(3): 40-42
- [10] 李云霞. 牙周病的病因及临床治疗研究进展[J].河北医学, 2013, 19 (3): 466-469
- Li Yun-xia. Research progress of etiology and clinical treatment of periodontal disease[J]. Hebei Medicine, 2013, 19(3): 466-469
- [11] 洪青梅. 机械刮治、根面平整联合药物在重症牙周炎治疗中的效果[J].现代诊断与治疗, 2015, 26(15): 3500-3501
- Hong Qing-ming. Clinical effect of Mechanical scraping, root surface smooth combined with drugs on Severe periodontitis [J]. Modern Diagnosis & Treatment, 2015, 26(15): 3500-3501
- [12] Fritoli A, Gonçalves C, Faveri M, et al. The effect of systemic antibiotics administered during the active phase of non-surgical periodontal therapy or after the healing phase: a systematic review[J]. J Appl Oral Sci, 2015, 23(3): 249-254
- [13] 傅晓幼,李国峰. 三种药物对牙周炎的临床疗效研究[J].南方医科大学学报, 2010, 30(03): 611-613
- Fu Xiao-you, Li Guo-feng. Therapeutic effects of three topical remedies on periodontitis [J]. Journal of Southern Medical University, 2010, 30(03): 611-613
- [14] 丁红柳,葛学军,曹艳. 甲硝唑牙周炎控缓药膜对慢性牙周病龈沟液基质金属蛋白 8 表达的影响[J].中国药物与临床, 2014, 14(11): 1585-1586
- Ding Hong-liu, Ge Xue-jun, Cao Yan. The influence of metronidazole controlled-release film to the expression of Gingival sulcus liquid MMP-8 in periodontal disease [J]. Chinese Remedies & Clinics, 2014, 14(11): 1585-1586
- [15] 郭爱玲,王晓琼,李宏. 甲硝唑控释药膜和盐酸米诺环素缓释剂治疗慢性牙周炎的效果分析[J].口腔医学, 2013, 33(009): 594-596
- Gui Ai-ling, Wang Xiao-qiong, Li Hong. The application and effect analysis of metronidazole controlled release pellicles and minocycline hydrochloride sustained-release agent on the treatment of chronic periodontitis[J]. Stomatology, 2013, 33(009): 594-596
- [16] 陈新,谭新伟,刘洪臣,等. 盐酸米诺环素联合替硝唑治疗 2 型糖尿病合并牙周病的临床研究 [J]. 现代药物与临床, 2014, 29(6): 664-667
- Chen Xin, Tan Xin-wei, Liu Hong-chen, et.al. Clinical study of minocycline combined with tinidazole in the treatment of type 2 diabetes with periodontal disease [J]. Drugs & clinic, 2014, 29(6): 664-667
- [17] 王萃萃. 盐酸米诺环素软膏联合甲硝唑药膜治疗牙周病的临床观察[J].北方药学, 2015, 12(10): 63
- Wang Cui-cui. Clinical effect of minocycline hydrochloride combined with metronidazole film on the treatment of periodontitis disease[J]. Journal of North Pharmacy, 2015, 12(10): 63
- [18] 李为. 盐酸米诺环素软膏治疗慢性牙周炎的临床观察 [J]. 安徽医学, 2012, 33(7): 826-827
- Li Wei. Clinical effect of minocycline hydrochloride ointment on periodontitis disease[J]. Anhui Medical Journal, 2012, 33(7): 826-827
- [19] 廖雪峰. 盐酸米诺环素软膏联合甲硝唑缓释药膜治疗慢性牙周炎的疗效观察[J]. 北华大学学报(自然科学版), 2014, 15(02): 229-232
- Liao Xue-feng. Curative Observation on Minocycline Hydrochloride Ointment in Combination with Metonidazole Sustained-Release Film on Chronic Periodontitis [J]. Journal of Beijing University (Natural Science), 2014, 15(02): 229-232
- [20] 顾蓉蓉. 盐酸米诺环素软膏联合甲硝唑药膜治疗牙周病的疗效和安全性研究[J].世界最新医学信息文摘:连续型电子期刊, 2016, 16 (24): 89+79
- Gu Rong-rong. Clinical effect and security of Minocycline Hydrochloride Ointment in Combination with Metonidazole Film on Chronic Periodontitis [J]. World Latest Medicine Information, 2016, 16(24): 89+79
- [21] Arun K V, Avaneendra T, Kumar T S S. T-helper cells in the etiopathogenesis of periodontal disease: A mini review [J]. Journal of Indian Society of Periodontology, 2011, 15(1): 4-10
- [22] 吕品,高津福. 细胞因子在牙周病和慢性阻塞性肺疾病中的作用 [J].牙体牙髓牙周病学杂志, 2007, 17(08): 485-488
- Ly Pin, Gao Jin-fu. The effect of cytokines on periodontal disease and chronic obstructive pulmonary disease [J]. Chinese Journal of Conservative Dentistry, 2007, 17(08): 485-488