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硫酸羟氯喹口服辅助治疗糜烂型口腔扁平苔癣的效果及对 AT-Ⅲ、ZAG 的影响 *

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摘要 目的：探讨硫酸羟氯喹口服辅助治疗糜烂型口腔扁平苔癣的效果及对人抗凝血酶Ⅲ（AT-Ⅲ）、锌 α2 糖蛋白（ZAG）的影响。**方法：**选择 2018 年 12 月 -2021 年 1 月在我院接受治疗的 115 例糜烂型口腔扁平苔癣患者，采用随机数表法分为治疗组（n=58）和对照组（n=57）。对照组给复方倍他米松治疗，治疗组在对照组的基础上联合硫酸羟氯喹口服治疗。比较两组临床疗效、AT-Ⅲ、ZAG、白细胞介素 4（IL-4）、白细胞介素 17（IL-17）、干扰素 γ（IFN-γ）、糜烂面积、疼痛评分水平变化情况及不良反应发生情况。**结果：**治疗后，两组总有效率比较差异显著（*P*<0.05）；治疗前，治疗组和对照组血清 AT-Ⅲ、ZAG 比较无显著差异；治疗后，治疗组和对照组血清 AT-Ⅲ、ZAG 均随着时间的推移而降低，且治疗组均低于对照组，差异显著（*P*<0.05）；治疗前，治疗组和对照组实验室指标水平比较无显著差异；治疗后，治疗组和对照组 IL-4、IL-17 均随着时间的推移而降低，且治疗组均低于对照组，IFN-γ 均随着时间的推移而升高，且治疗组均高于对照组，差异显著（*P*<0.05）；治疗前，治疗组和对照组糜烂面积、疼痛评分比较无显著差异；治疗后，治疗组和对照组糜烂面积、疼痛评分均随着时间的推移而降低，且治疗组均低于对照组，差异显著（*P*<0.05）；两组不良反应总发生率为 3.45%、8.77%，无显著差异（*P*>0.05）。**结论：**在糜烂型口腔扁平苔癣中应用硫酸羟氯喹口服辅助治疗疗效显著，可有效改善患者 AT-Ⅲ、ZAG 水平。

关键词：硫酸羟氯喹；辅助治疗；糜烂型口腔扁平苔癣；人抗凝血酶Ⅲ；锌 α2 糖蛋白

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Effect of Oral Adjuvant Treatment of Erosive Oral Lichen Planus with Hydroxychloroquine Sulfate and Its Effect on AT-Ⅲ and ZAG*

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ABSTRACT Objective: To study Effect of oral adjuvant treatment of erosive oral lichen planus with hydroxychloroquine sulfate and its effect on Human antithrombin Ⅲ (at-Al), zinc α2 glycoprotein (Zag). **Methods:** 115 patients with eroded oral lichen planus treated in our hospital from December 2018 to January 2021 were selected and divided into treatment group (n=58) and control group (n=57) by random number table method. The control group was treated with compound betamethasone, and the treatment group was combined with oral treatment of hydroxychloroquine sulfate on the basis of the control group. The clinical efficacy, AT-Ⅲ, Zag, interleukin-4 (IL-4), interleukin-17 (IL-17), interferon γ (IFN-γ), erosion area, pain score changes and the incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate between the two groups was significantly different (*P*<0.05). Before treatment, there were no significant differences between the treatment group and the control group in serum AT-Ⅲ and Zag. After treatment, serum AT-Ⅲ and Zag in treatment group and control group decreased with the passage of time, and treatment group was lower than control group, the differences were significant (*P*<0.05). Before treatment, there was no significant difference in the laboratory index levels between the treatment group and the control group. After treatment, IL-4 and IL-17 in treatment group and control group decreased with the passage of time, and the treatment group was lower than the control group, IFN-γ increased with the passage of time, and the treatment group was higher than the control group, the difference was significant(*P*<0.05); Before treatment, there were no significant differences in erosion area and pain score between the treatment group and the control group. After treatment, erosion area and pain score of both treatment group and control group decreased with the passage of time, and the treatment group was lower than the control group, the differences were significant(*P*<0.05). The total incidence of adverse reactions between the two groups was 3.45% and 8.77%, with no significant difference (*P*>0.05). **Conclusion:** Oral adjuvant treatment of erosive oral lichen planus with hydroxychloroquine sulfate is effective, which can effectively improve the levels of AT-Ⅲ and Zag in patients.

Key words: Hydroxychloroquine sulfate; Adjuvant therapy; Erosive oral lichen planus; Human antithrombin Ⅲ; Zinc α2 glycoprotein

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前言

口腔扁平苔癣是一种慢性炎症疾病，患病率约为 0.1%~4%,可发生在口腔黏膜的任何部位,临床表现为糜烂、白色花纹病损等症状[1,2]。口腔扁平苔癣主要分萎缩型和糜烂型两种，其中糜烂型的发病率高于萎缩型，癌变率高达 0.9%～19.8%，对患者生命造成威胁[3,4]。复方倍他米松是一种糖皮质激素,具有抗炎、抗风湿的作用,对口腔扁平苔藓具有一定的治疗效果[5]。但有研究显示,糜烂型口腔扁平苔癣发病机制较为复杂,单纯使用糖皮质激素治疗达不到预期治疗效果,需其他药物辅助治疗提高疗效[6]。硫酸羟氯喹是皮肤科常用药物,有免疫抑制及抗炎作用,近年来被广泛用于口腔扁平苔癣的治疗中[7]。有研究显示,糜烂型口腔扁平苔癣在病变过程中可导致部分蛋白发生变化，其中可表现出 AT-Ⅲ、ZAG 异常升高，因此探讨 AT-Ⅲ、ZAG 在治疗前后的变化,对评估治疗方法具有重要意义[8]。本研究旨在探讨硫酸羟氯喹口服辅助治疗糜烂型口腔扁平苔癣的效果及对 AT-Ⅲ、ZAG 的影响。

1 资料与方法

1.1 一般资料

选择 2018 年 12 月 -2021 年 1 月在我院接受治疗的 115 例糜烂型口腔扁平苔癣患者,采用随机数表法分为 2 组,治疗组 58 例,男 25 例,女 33 例,年龄 22~65 岁,平均(46.15± 3.16)岁,病程 3 月 ~3 年,平均(1.89± 0.35)年。对照组 57 例,男 20 例,女 37 例,年龄 23~66 岁,平均(46.21± 3.17)岁,病程 4 月 ~3.5 年,平均(1.93± 0.38)年。两组一般资料无显著差异(P>0.05),可比较。

参照《口腔扁平苔藓诊疗指南》[9]中的诊断标准;临床症状伴有糜烂;病理组织确诊。

纳入标准:(1)符合相关标准;(2)肝肾功能正常;(3)无胰岛素治疗史;(4)相关指标数据完整;(5)知情同意。排除标准:(1)其他口腔疾病者;(2)心功能异常者;(3)近 3 个月有抗生素治疗者;(4)严重自身免疫性疾病;(5)妊娠、哺乳期者;(6)对本研究药物过敏者;(7)其他因素导致扁平苔癣者。

1.2 方法

对照组给予复方倍他米松(规格 0.5 g,厂家:中美上海施贵宝制药有限公司,国药准字 H20023370)1 mL 在病变粘膜处多点注射治疗,1 周 1 次。治疗组在对照组的基础上给予硫酸羟氯喹:(规格:0.5 μg; 生产厂家:Baxtcr Pharmaccutical Solutions LLC;国药准字:JX20080117)200 mg,口服,每日 2 次。

1.3 观察指标

采集肘静脉血 4 mL,采用酶联免疫吸附试验测定 AT-Ⅲ、ZAG、IL-4、IL-17、IFN-γ 水平;记录患者糜烂面积、疼痛评分变化情况;记录不良反应。

疗效评定标准:显效:临床症状消失,白色条纹及疼痛消失;有效:症状消失,糜烂面积显著缩小;无效:无明显改善或加重。

1.4 统计学分析

以 spss22.0 软件包处理,符合正态分布计量资料用均数± 标准差($\bar{x}\pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示,x^2 检验, P＜0.05 表示差异具有统计学意义。

2 结果

2.1 两组临床治疗效果评价

治疗后,两组总有效率比较差异显著(P<0.05)见表 1。

表 1 两组临床治疗效果评价[n(%)]

Table 1 Clinical therapeutic effect evaluation of the two groups[n(%)]

Groups	n	Excellent	Valid	Invalid	Total effective rate
Treatment group	58	29(50.00)	25(43.10)	4(6.90)	54(93.10)
Control group	57	27(47.37)	18(31.58)	12(21.05)	45(78.95)
x^2 value					4.809
P value					0.028

2.2 两组 AT-Ⅲ、ZAG 检查结果比较

治疗前，治疗组和对照组血清 AT-Ⅲ、ZAG 比较无显著差异;治疗后,治疗组和对照组血清 AT-Ⅲ、ZAG 均随着时间的推移而降低,且治疗组均低于对照组,差异显著(P<0.05),见表 2。

表 2 两组 AT-Ⅲ、ZAG 检查结果比较($\bar{x}\pm s$)

Table 2 Comparison of AT-Ⅲ and ZAG test results between the two groups($\bar{x}\pm s$)

Groups	n	AT-Ⅲ(μg/L)		ZAG(mg/L)	
		Before the intervention	After the intervention	Before the intervention	After the intervention
Treatment group	58	161.98± 18.35	130.74± 14.25	65.97± 6.85	38.05± 4.35
Control group	57	162.09± 18.56	141.56± 15.41	66.15± 6.93	44.15± 4.67
t value		0.032	3.910	0.140	7.249
P value		0.975	0.000	0.889	0.000

2.3 两组实验室指标水平比较

治疗前，治疗组和对照组实验室指标水平比较无显著差异；治疗后，治疗组和对照组 IL-4、IL-17 均随着时间的推移而降低，且治疗组均低于对照组，IFN-γ 均随着时间的推移而升高，且治疗组均高于对照组，差异显著（P<0.05），见表 3。

表 3 两组实验室指标水平比较（$\bar{x}\pm s$，ng/L）

Table 3 Comparison of laboratory index levels between the two groups（$\bar{x}\pm s$, ng/L）

Groups	n	IL-4		IL-17		IFN-γ	
		Before the intervention	After the intervention	Before the intervention	After the intervention	Before the intervention	After the intervention
Treatment group	58	0.39± 0.10	0.11± 0.02	0.44± 0.15	0.17± 0.03	0.24± 0.08	0.54± 0.11
Control group	57	0.38± 0.14	0.26± 0.05	0.45± 0.12	0.30± 0.09	0.22± 0.10	0.40± 0.07
t value		0.441	21.189	0.394	10.428	1.185	8.127
P value		0.659	0.000	0.694	0.000	0.238	0.000

2.4 两组糜烂面积、疼痛评分比较

治疗前，治疗组和对照组糜烂面积、疼痛评分比较无显著差异；治疗后，治疗组和对照组糜烂面积、疼痛评分均随着时间的推移而降低，且治疗组均低于对照组，差异显著（P<0.05），见表 4。

表 4 两组糜烂面积、疼痛评分比较（$\bar{x}\pm s$）

Table 4 Comparison of erosion area and pain scores between the two groups（$\bar{x}\pm s$）

Groups	n	Erosion area（mm^2）		VASscore（points）	
		Before the intervention	After the intervention	Before the intervention	After the intervention
Treatment group	58	48.71± 5.04	5.74± 0.73	8.15± 0.78	0.71± 0.04
Control group	57	49.05± 5.13	9.68± 0.96	8.19± 0.67	1.85± 0.16
t value		0.359	24.801	0.295	52.619
P value		0.721	0.000	0.769	0.000

2.5 安全性评价

两组不良反应总发生率为 3.45%、8.77%，无显著差异（P>0.05），见表 5。

表 5 安全性评价[n(%)]

Table 5 Safety evaluation[n(%)]

Groups	n	Taste is changed	Blurred vision	Gastrointestinal discomfort	The total incidence of
Treatment group	58	2	0	0	2(3.45)
Control group	57	1	2	2	5(8.77)
x^2 value					1.425
P value					0.233

3 讨论

糜烂型口腔扁平苔癣是口腔科常见疾病，多发生于 50~55 岁，女性发病率高于男性，该病具有反复发作、迁延难愈等特点，若得不到有效治疗在一定程度上可造成癌变，影响患者的健康[10-14]。糜烂型口腔扁平苔癣的发病机制较为复杂，可能与免疫紊乱、感染等因素有关[15]。临床常用糖皮质激素治疗该病，复方倍他米松是常见的糖皮质激素，主要成分为二丙酸倍他米松和倍他米松磷酸钠，其中倍他米松磷酸钠溶解性好，起效快，二丙酸倍他米松则可缓慢进入组织，具有抗菌消炎、免疫抑制等作用，可减轻口腔内炎症，缓解临床症状[16-19]。但有研究显示，糖皮质激素疗效维持时间较短，停药后易复发，且有一定副作用，不宜长期服用，需与其他药物联合治疗提高临床疗效[20]。

有学者认为，糜烂型口腔扁平苔癣发病可能与免疫紊乱有关，因此给予免疫调节剂治疗对疾病具有一定作用[21]。硫酸羟氯喹是一种 4- 氨基喹啉类化合物，具有免疫抑制作用，能抑制多种细胞因子的分泌，缓解细胞损伤，与口腔扁平苔藓的病机吻合[22,23]。国外研究显示，硫酸羟氯喹可经提高细胞溶酶体膜的稳定性，抑制溶酶体分泌，消除炎症反应，缓解口腔扁平苔藓临床症状[24]。本研究结果显示，两种药物联合治疗的患者总有效

率较单独使用复方倍他米松的高，提示，联合治疗能提高临床疗效，Dds D[25]等研究也显示，硫酸羟氯喹辅助治疗糜烂型口腔扁平苔癣效果显著，能提高治疗效果，对促进患者恢复具有重要意义。

有研究显示，糜烂型口腔扁平苔癣可导致相关细胞因子发生改变[26]。AT-Ⅲ是机体重要的抗凝蛋白，可控制纤维蛋白溶解，同时还可结合凝血酶，引起凝血酶变性，在多种疾病中表达异常[27]。近年来有研究显示，AT-Ⅲ可降低炎症细胞活性，诱导生成抗炎物质，同时还能抑制细胞因子等物质生成，缓解炎症反应，可能参与了糜烂型口腔扁平苔癣的发展[28]。ZAG 为脂肪调节因子，由多种腺上皮细胞、皮下和内脏的脂肪组织分泌，可通过增加胰岛素敏感性，提高组织葡萄糖代谢率，降低脂肪含量，同时还能促进脂肪分解，起到抗肥胖的作用，被认为参与脂代谢调节过程，与多种恶病质疾病及心血管疾病发生有关[29,30]。Qataya P O[31]等研究显示，ZAG 在 2 型糖尿病中水平升高，且与胰岛素抵抗呈负相关。有研究显示，ZAG 可经识别免疫因子参与免疫应答，与恶性肿瘤的发生关系密切[32]。国外研究显示，AT-Ⅲ、ZAG 在糜烂型口腔扁平苔癣的恶性病变中表达异常升高，可能与机体免疫异常有关[33]。本研究将 AT-Ⅲ、ZAG 作为参与糜烂型口腔扁平苔癣的重要指标，观察在不同治疗方案中其水平变化，结果显示，治疗后患者 AT-Ⅲ、ZAG 明显降低，且硫酸羟氯喹联合复方倍他米松治疗的患者低于单独使用复方倍他米松的患者，提示，糜烂型口腔扁平苔癣患者机体存在较强的免疫炎症反应，而硫酸羟氯喹联合复方倍他米松联合治疗能降低 AT-Ⅲ、ZAG 水平。本研究还显示，治疗后，患者 IL-4、IL-17 明显降低，且治疗组均低于对照组，IFN-γ 明显升高，且治疗组均高于对照组，进一步提示了硫酸羟氯喹联合复方倍他米松可抑制机体炎症反应，纠正炎性因子异常改变。Wang L [34]等研究也显示，硫酸羟氯喹可通过抑制蛋白合成，阻断白介素的产生，降低机体炎症反应。分析其原因可能是因为硫酸羟氯喹可阻断 T 细胞的激活，促进降低中心粒细胞、巨噬细胞，达到抑制 T 细胞介导的免疫活化，从而降低体内炎症反应。本研究结果还显示，治疗后患者糜烂面积、疼痛评分明显降低，且硫酸羟氯喹联合复方倍他米松治疗的患者低于对照组，且联合治疗具有较高的安全性，不会增加不良反应发生率。提示，硫酸羟氯喹在糜烂型口腔扁平苔癣中效果显著，可促进糜烂型口腔扁平苔癣创面修复，缓解疼痛。Hrmda B[35]等研究也显示，硫酸羟氯喹在糜烂型口腔扁平苔癣中的效果明显，能促进创面修复。分析其原因可能是因为硫酸羟氯喹可促进分泌胰岛素，抑制胰岛素分解，降低血糖水平，从而缓解机体氧化应激，促进溃疡面愈合。

综上所述，在糜烂型口腔扁平苔癣中应用硫酸羟氯喹口服辅助治疗疗效显著，可有效改善患者 AT-Ⅲ、ZAG 水平。

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