

doi: 10.13241/j.cnki.pmb.2020.15.035

## 康复新液与他克莫司联合沙利度胺治疗口腔扁平苔藓的疗效及安全性分析\*

刘晓慧<sup>1</sup> 刘永红<sup>2</sup> 张晓光<sup>3</sup> 于倩<sup>1</sup> 魏雅楠<sup>4</sup>

(1 河北医科大学沧州中西医结合临床医学院口腔门诊 河北 沧州 061000;

2 河北医科大学第二医院口腔内科 河北 石家庄 050000; 3 河北医科大学第二医院皮肤性病科 河北 石家庄 050000;

4 河北医科大学沧州中西医结合临床医学院中医内科 河北 沧州 061000)

**摘要** 目的:探讨康复新液与他克莫司联合沙利度胺治疗口腔扁平苔藓(oral lichen planus, OLP)的临床疗效及安全性。方法:选择2017年12月-2020年1月就诊于我院的80例OLP患者,采用随机数字表法将其分为联合组和对照组,每组40例。两组均进行常规治疗,对照组使用0.1%的他克莫司软膏与康复新液治疗,联合组在对照组的基础上加用沙利度胺片,比较两组的临床疗效、治疗前后糜烂面大小、疼痛程度的变化以及不良反应的发生情况。结果:治疗后,联合组总有效率为90.00%,显著高于对照组(72.5%,  $P>0.05$ );与治疗前相比,两组口腔糜烂面积和疼痛程度均显著降低( $P<0.05$ ),且联合组口腔糜烂面积和疼痛程度显著低于对照组( $P<0.05$ );治疗期间,对照组出现1例不良反应,具体表现为轻微的黏膜烧灼痛,停药后两天后症状消失,不良反应发生率为2.5%,联合组出现2例不良反应,其中1例病变部位出现黏膜萎缩,1例出现色素沉着,不良反应发生率为5.0%,两组不良反应的发生率比较无显著差异( $P>0.05$ )。结论:康复新液与他克莫司联合沙利度胺治疗口腔扁平苔藓的临床疗效明显优于康复新液与他克莫司治疗,其能明显降低黏膜糜烂面积和疼痛程度,且安全性高。

**关键词:**他克莫司;康复新液;沙利度胺;口腔扁平苔藓;临床疗效;安全性

**中图分类号:**R781.5 **文献标识码:**A **文章编号:**1673-6273(2020)15-2971-04

## Efficacy and Safety of Kangfuxin Solution and Tacrolimus Combined with Thalidomide in the Treatment of Oral Lichen Planus\*

LIU Xiao-hui<sup>1</sup>, LIU Yong-hong<sup>2</sup>, ZHANG Xiao-guang<sup>3</sup>, YU Qian<sup>1</sup>, WEI Ya-nan<sup>4</sup>

(1 Department of Stomatology, Cangzhou Medical College of Integrated Traditional Chinese and Western Medicine, Hebei Medical University, Cangzhou, Hebei, 061000, China; 2 Department of Stomatology, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050000, China; 3 Department of Dermatology and Venereology, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050000, China; 4 Department of Traditional Chinese Medicine, Cangzhou Medical College of Integrated Traditional Chinese and Western Medicine, Hebei Medical University, Cangzhou, Hebei, 061000, China)

**ABSTRACT** **Objective:** To investigate the clinical efficacy and safety of Kangfuxin solution and tacrolimus combined with thalidomide in the treatment of oral lichen planus. **Methods:** Eighty patients with OLP who were treated in our hospital from December 2017 to January 2020 were selected and divided into the combined group and the control group by a random number table method, with 40 cases in each group. Both groups were given routine treatment, the control group was treated with 0.1% tacrolimus ointment and Kangfuxin solution, and the combined group was given thalidomide tablets on the basis of control group. The clinical efficacy, size of the eroded surface, degree of pain before and after treatment and the occurrence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate of combined group was 90.00%, which was significantly higher than that of the control group (72.5%,  $P>0.05$ ). Compared with before treatment, the area of oral erosion and the degree of pain in both groups were significantly reduced ( $P<0.05$ ), which were significantly lower in the combined group than those of the control group ( $P<0.05$ ). During the treatment period, one cases of adverse reaction was found in the control group, which was manifested as mild mucosal burning pain. The symptoms disappeared two days after the drug was stopped. The incidence of adverse reactions was 2.5%. There were two cases of adverse reactions in the combined group, including 1 case of mucosal atrophy at the lesion site and 1 case of pigmentation, and the incidence of adverse reactions was 5.0%. There was no significant difference in the incidence of adverse reactions between the two groups ( $P>0.05$ ). **Conclusion:** The clinical efficacy of Kangfuxin solution combined with tacrolimus combined with thalidomide in the treatment of oral lichen planus was significantly better than that of Kangfuxin solution combined with tacrolimus, which could significantly reduce the mucosal erosion area and pain with high safety.

\* 基金项目:国家自然科学基金青年基金项目(81700948)

作者简介:刘晓慧(1977-),女,硕士研究生,副主任医师,研究方向:口腔临床医学,电话:13833998086, E-mail: WangjunEvaxiangbao@163.com

(收稿日期:2020-03-11 接受日期:2020-03-31)

**Key words:** Tacrolimus; Kangfuxin solution; Thalidomide; Oral lichen planus; Clinical efficacy; Safety

**Chinese Library Classification(CLC):** R781.5 **Document code:** A

**Article ID:**1673-6273(2020)15-2971-04

## 前言

口腔扁平苔藓(Oral lichen planus, OLP)是一种常见的口腔黏膜疾病,可累及皮肤,以中年女性较为多见,病损大多左右对称,包括网状损害、斑块型、萎缩型、糜烂型、丘疹型等<sup>[1-4]</sup>。其中,糜烂型病损如果长期不能有效治愈,有恶变的可能性,WHO 将其列为癌前状态<sup>[5]</sup>。扁平苔藓的发生与多方面原因有关,如心理因素、内分泌系统功能紊乱、免疫系统失调、外界感染、微循环障碍以及遗传因素等,但由于病因不明,临床尚未有能彻底治疗扁平苔藓的药物<sup>[6,7]</sup>。目前对 OLP 的治疗多采用调节患者的机体免疫功能的方法,常用方法包括糖皮质激素类药物<sup>[8]</sup>,免疫抑制剂(他克莫司、吗替麦考酚酯以及环孢素等)<sup>[9]</sup>,维 A 酸<sup>[10]</sup>,低分子量肝素<sup>[11]</sup>,抗病毒类药物<sup>[12]</sup>,紫外线治疗<sup>[13]</sup>,中医药治疗等<sup>[14]</sup>。有全身应用和局部应用的区别,但是单纯局部用药或全身用药的临床疗效不甚理想。

他克莫司为大环内酯类免疫抑制剂,对 OLP 的疗效较好,且不会抑制胶原的合成,对于皮质类固醇激素无效的 OLP 有良好的效果,短期使用引起皮肤萎缩的可能性较小<sup>[15]</sup>。康复新

液是一种外科常用药,具有各种多元醇类、表皮生长因子、氨基酸、黏糖氨酸等多种氨基酸活性物质,用于外伤、烧伤、溃疡等创面,有抗炎、消肿、促进细胞增殖和新生肉芽组织增长,迅速修复损伤的皮肤黏膜,加快坏死组织的脱落,同时也能提高机体的免疫力,促进溃疡愈合<sup>[16]</sup>。沙利度胺为人工合成的谷氨酸衍生物,口服后没有明显的肝脏代谢,主要通过非酶的水解作用清除,具有免疫调节、抗炎和抑制血管生成等作用<sup>[17,18]</sup>。因此,本研究采用康复新液和他克莫司联合沙利度胺治疗 OLP,探讨了其临床疗效及安全性,旨在为临床治疗 OLP 提供一定的参考依据,结果报道如下。

## 1 对象和方法

### 1.1 基本信息

选择 2017 年 12 月-2020 年 1 月就诊于我院的 80 例 OLP 患者,采用随机数字表法分为联合组和对照组,每组各 40 例。两组的基本资料对比差异无统计学意义( $P>0.05$ ),有可比性,见表 1。患者及家属签署知情同意书,本研究已获得医院伦理委员会的准许。

表 1 两组基本资料的比较

Table 1 Comparison of basic data between two groups

| Groups               | Age(years) |             | Gender |        | Erosion area (cm <sup>2</sup> ) |
|----------------------|------------|-------------|--------|--------|---------------------------------|
|                      | Age range  | Average age | Male   | Female |                                 |
| Control group (n=40) | 41~65      | 51.3±7.8    | 8      | 32     | 0.92±0.41                       |
| Joint Group (n=40)   | 42~63      | 52.1±6.6    | 6      | 34     | 1.08±0.70                       |

### 1.2 纳入标准

① 经病理检查并确诊为 OLP;② 治疗前未接受任何激素以及免疫抑制剂的治疗;③ 未接受局部用药;④ 无其他口腔黏膜或牙周疾病。

### 1.3 排除标准

① 患有免疫性疾病,对疗效有影响者;② 治疗前一天使用过镇痛药者;③ 肝脏功能异常及患有糖尿病、高血压基础性病患者;④ 妊娠、哺乳期或近期有生育计划的妇女;⑤ 对他克莫司及沙利度胺等过敏者。

### 1.4 治疗方法

联合组和对照组均进行常规治疗。日常保持口腔卫生,改善饮食结构,治疗期不食辛辣以及过冷过热食物,改变不良生活习惯,维持积极健康的心态,保持良好的睡眠,使用 3%碳酸氢钠和口洁素溶液交替漱口,饭后口腔清洁后含漱,3 次/日;进行全口洁治,拔除口腔内的残根残冠,调磨牙冠锐利边缘,防止影响黏膜愈合。

对照组使用 0.1%的他克莫司软膏和康复新液治疗,0.1%的他克莫司软膏用无菌棉签取适量,在颊黏膜病损区域表面轻轻均匀的涂层一薄层,1 h 内不要饮水、进食及讲话,三餐后及睡前用药,连用 4 w。康复新液每天在三餐后含漱,每次含

5 min。联合组在对照组的基础上加用沙利度胺片,每晚睡前口服 100 mg,待症状缓解后调整为 50 mg,治疗 4 w。

### 1.5 观察指标

1.5.1 疗效判断标准 对每个患者的检查、评分及记录均由两位医生共同评议完成。各项指标分值相加,对其总分进行疗效评价,评价指标及标准<sup>[19]</sup>,见表 2。

痊愈:总分为 0 分;显效:总分为 1~3 分;有效:总分为 4~5 分;无效:总分>6 分;计算总有效率。总有效率=(痊愈+显效+有效)/总例数×100%。

1.5.2 糜烂面大小和疼痛程度 记录治疗前后 OLP 患者糜烂面大小的变化;采用视觉刻度评估法(VAS)记录疼痛程度,由患者进行评估,评分范围为 0~10 分,无痛记 0 分,轻微疼痛记 1~3 分,疼痛影响睡眠但是能忍受剂 4~6 分,疼痛剧烈难以忍受记 7~10 分,数值越大疼痛程度越重。

1.5.3 不良反应 记录患者治疗期间发生的不良反应,如胃肠症状、尿量增多、失眠头痛以及皮下出血等症状。

### 1.6 统计学分析

数据应用 SPSS 19.0 进行统计学分析,计量资料以  $\bar{x} \pm s$  表示,组间比较用 t 检验,计数资料以率(%)表示,组间比较使用  $\chi^2$  检验,以  $P<0.05$  为差异有统计学意义。

表 2 评价指标及标准  
Table 2 Evaluation indicators and standards

| Index                   | Score     |           |               |                         |           |
|-------------------------|-----------|-----------|---------------|-------------------------|-----------|
|                         | 4         | 3         | 2             | 1                       | 0         |
| White lesion appearance | /         | Aggravate | No change     | Lighten                 | disappear |
| Lesion size             | Aggravate | No change | Less than 50% | Reduce by more than 50% | disappear |
| Discomfort (symptoms)   | /         | Aggravate | No change     | Lighten                 | disappear |

## 2 结果

治疗后,联合组的总有效率为 90.00%,显著高于对照组(72.50%, $P>0.05$ ),见表 3。

### 2.1 两组临床疗效的比较

表 3 两组临床疗效的比较(例,%)  
Table 3 Comparison of clinical efficacy between two groups(n,%)

| Groups               | Healed | Significant effective | Effective | Invalid | Total effective |
|----------------------|--------|-----------------------|-----------|---------|-----------------|
| Control group (n=40) | 6      | 10                    | 13        | 13      | 29 (72.50)      |
| Joint group (n=40)   | 9      | 12                    | 15        | 4       | 36 (90.00)      |

### 2.2 两组治疗前后糜烂面积和疼痛程度的比较

与治疗前相比,两组口腔糜烂面积和疼痛程度均显著降低

( $P<0.05$ ),与对照组相比,联合组口腔糜烂面积和疼痛程度显著降低( $P<0.05$ ),见表 4。

表 4 两组治疗前后糜烂面积大小和疼痛程度的比较

Table 4 Comparison of the size and pain degree of erosion area before and after treatment between two groups

| Groups               | Erosion size     |                 | VAS Score        |                 |
|----------------------|------------------|-----------------|------------------|-----------------|
|                      | Before treatment | After treatment | Before treatment | After treatment |
| Control group (n=40) | 9.31±0.45        | 0.71±0.21*      | 7.45±0.51        | 3.93±0.21*      |
| Joint group (n=40)   | 9.28±0.23        | 0.18±0.33**     | 7.30±0.26        | 2.08±0.19**     |

Note: \*  $P<0.05$  compared with before treatment; \*\* $P<0.05$  compared with the control group.

### 2.3 两组不良反应发生情况的比较

治疗期间,对照组出现 1 例不良反应,具体表现为轻微的黏膜烧灼痛,停药后两天后症状消失,不良反应的发生率为 2.5%;联合组出现 2 例不良反应,其中 1 例病变部位出现黏膜萎缩,1 例出现色素沉着,不良反应发生率为 5.0%。两组不良反应的发生率比较无显著差异( $P>0.05$ )。

## 3 讨论

目前,OLP 的病因尚未完全清楚,病理检查显示扁平苔藓其上皮固有层出现大量呈密集带状浸润的淋巴细胞,以 T 淋巴细胞为主,表明 OLP 有可能是一种免疫反应性疾病<sup>[20]</sup>。国内外多采用激素类药物和免疫抑制剂治疗 OLP,但肾上腺皮质激素存在一定的不足,疗程较长,长期使用可能会导致代谢紊乱等多种不良反应,局部黏膜萎缩变硬等,甚至会发生真菌感染<sup>[21-24]</sup>。因此,亟待寻找对 OLP 疗效确切且安全性高的治疗方法。

他克莫司为一种强效的免疫抑制剂(钙调神经磷酸酶抑制剂),可抑制 T 淋巴细胞活化,其免疫抑制作用是环孢素 A 的 10~100 倍,且分子量小,易于穿透。局部使用对浸渍性扁平苔藓以及溃疡期坏疽脓皮病均有较好的疗效<sup>[25-27]</sup>。他克莫司主要作用于 T 淋巴细胞,可与特异胞浆蛋白和 FK-506 蛋白紧密结合,抑制 T 细胞的产生;他克莫司可以活化 T 细胞核因子靶位,细胞核因子可调控 mRNA 的各种介质,诱导淋巴细胞细胞

素转录,因其分子量较小,血液中一般难以检测出药物,全身治疗不良反应发生率极小,长期使用局部可能会产生灼烧感,但会随着黏膜损伤程度的好转而减轻<sup>[28,29]</sup>。

OLP 患者血清 TNF- $\alpha$  水平高于正常人<sup>[30]</sup>,上调 IL-6 和免疫球蛋白水平,导致 OLP 活动期与静止期交替出现。沙利度胺为谷氨酸衍生物,药代动力学显示口服后没有明显的肝脏代谢现象,主要通过非酶的水解作用清除。沙利度胺可降解 TNF- $\alpha$  的 mRNA,进而减少 TNF- $\alpha$  的合成,起到免疫调节的作用。沙利度胺还可阻断炎症基因的表达,抑制血管的生成,可能会导致轻微的淋巴细胞减少,停药后可逐渐消失。康复新液可抗炎、消肿、促进细胞增殖和新生肉芽组织增长,迅速修复损伤的皮肤黏膜,加快坏死组织的脱落,同时也能提高机体的免疫力,进而促进口腔扁平苔藓患者黏膜糜烂的康复<sup>[31]</sup>。本研究采用康复新液与他克莫司联合沙利度胺治疗 OLP,总有效率显著高于对照组,表明康复新液与他克莫司联合沙利度胺治疗 OLP 具有协同增效的作用,能显著提高治疗 OLP 的总有效率。

OLP 患者口腔常有黏膜糜烂症状,在进食、吞咽时常引起局部烧灼感、疼痛感等,给患者的生活和健康等方面带来了极大的影响。VAS 评分为一种评价由各种疾病引起的疼痛程度的工具。本研究中,与对照组相比,联合组患者口腔糜烂面积和疼痛程度减少更显著。显示康复新液与他克莫司联合沙利度胺治疗 OLP 可以显著改善患者的临床症状和疼痛程度,改善患

者的生活质量。同时,对照组治疗期间出现 1 例不良反应,与联合组比较无显著差异,提示康复新液与他克莫司联合沙利度胺治疗 OLP 并未增加治疗时的风险,安全性较好。

综上所述,康复新液与他克莫司联合沙利度胺治疗口腔扁平苔藓的临床疗效明显优于康复新液与他克莫司治疗,其能明显降低粘膜糜烂面积和疼痛程度,且安全性高。

#### 参考文献(References)

- [1] Giannetti L, Diago AMD, Spinas E. Oral Lichen planus [J]. J Biol Regul Homeost Agents, 2018, 32(2): 391-395
- [2] Masquijo-Bisio PA, Gandolfo MS, Keszler A, et al. Usefulness of a direct immunofluorescence in the diagnosis of plaque type oral lichen planus[J]. Ann Diagn Pathol, 2017, 31: 20-22
- [3] Mutaftchieva MZ, Draganova-Filipova MN, Zagorchev PI, et al. Effects of Low Level Laser Therapy on Erosive-atrophic Oral Lichen Planus [J]. Folia Med, 2018, 60(3): 417-424
- [4] A Shiva, A Zamanian, S Arab, et al. Immunohistochemical Study of p53 Expression in Patients with Erosive and Non-Erosive Oral Lichen Planus[J]. J Dent, 2018, 19(2): 118-123
- [5] Li XZ, Yang XY, Wang Y, et al. Urine metabolic profiling for the pathogenesis research of erosive oral lichen planus[J]. Arch Oral Biol, 2017, 73: 206-213
- [6] Wiriyakijja P, Porter S, Fedele S, et al. Validation of the HADS and PSS 10 and psychological status in patients with oral lichen planus[J]. Oral Dis, 2020, 26(1): 96-110
- [7] Thongprasom, K. Oral lichen planus: Challenge and management[J]. Oral Dis, 2018, 24(1-2): 172-173
- [8] 张琳, 刘一平, 陶洋, 等. 白芍总苷联合曲安奈德对口腔扁平苔藓患者的临床疗效及其对血清 TNF- $\alpha$  和 IL-6 水平的影响[J]. 川北医学院学报, 2019, 34(6): 686-689
- [9] Mateeva V, Vassileva S. Lichen Planus and Lichenoid Disorders[M]// Advances in Integrative Dermatology. John Wiley & Sons, Ltd, 2019
- [10] Mahdi KA. Comparative Effect of Topical Tacrolimus and Topical Isotretinoin in Patients with Oral Lichen Planus [J]. Indian J Pub Health Res and Dev, 2019, 10(2): e693
- [11] Dunaway S, Tyler K, Kaffenberger J. Update on treatments for erosive vulvovaginal lichen planus [J]. Int J Dermatol, 2020, 59(3): 297-302
- [12] Gupta A, Sardana K, Arora P, et al. Extensive hypopigmented cribriform lesions with fine scaling in a child [J]. Pediatr Dermatol, 2018, 35(3): 410-412
- [13] Tan Z, Li J, Zhang X, et al. TP53 Promotes Retinoid Acid-induced Smooth Muscle Cell Differentiation by Targeting Myocardin[J]. Stem Cells Dev, 2018, 27(8): 534-544
- [14] Muhammad K, Faisal J, Terence O, et al. Oral Xa Inhibitors versus low molecular weight heparin for thromboprophylaxis after nonoperative spine trauma[J]. J Surg Res, 2018, 232: 82-87
- [15] 凌诗琪, 宗文凯. 他克莫司软膏在皮肤科的主要临床应用[J]. 中国皮肤性病学杂志, 2018, 32(8): 950-954
- [16] 郑宇杰. 康复新液联合曲安奈德局部注射治疗糜烂型口腔扁平苔藓的疗效分析[J]. 全科口腔医学电子杂志, 2019, 6(35): 176-177
- [17] 毛海燕, 刘斯平, 汪竹, 等. 肝转移癌化疗联合沙利度胺治疗临床疗效与不良反应观察[J]. 中华肿瘤防治杂志, 2019, 22(8): 559-564
- [18] Aguh C, Kwatra SG, He A, et al. Thalidomide for the treatment of chronic refractory prurigo nodularis [J]. Dermatol Online J, 2018, 24(3): e13030
- [19] 赵莉. 口腔黏膜病临床治疗 IV. 口腔扁平苔藓的诊断及治疗研究[J]. 中国医药指南, 2019, 17(20): 118-119
- [20] Sisti A, Fallaha A, Tassinari J, et al. Melanoma in situ mimicking a Lichen planus-like keratosis[J]. Acta Biomed, 2018, 88(4): 496-498
- [21] Dario Di Stasio, Agostino Guida, Carmen Salerno, et al. Oral lichen planus: a narrative review[J]. Front Biosci (Elite Ed), 2014, 6: 370-376
- [22] Kousuke, Matsumoto, Kenji, et al. Clinical Evaluation of CO<sub>2</sub> Laser Vaporization Therapy for Oral Lichen Planus: A Single-Arm Intervention Study[J]. Photobiomodul Photomed Laser Surg, 2019, 37(3): 175-181
- [23] Antonio, Marcondes, Lerario, et al. Molecular Mechanisms of Stem/Progenitor Cell Maintenance in the Adrenal Cortex [J]. Front in Endocrinol, 2017, 8: e52
- [24] Shimada H, Noro E, Suzuki S, et al. Effects of Adipocyte-derived Factors on the Adrenal Cortex [J]. Curr Mol Pharmacol, 2020, 13(1): 2-6
- [25] Jin L, Lim SW, Jin J, et al. Effect of Conversion to CTLA4Ig Treatment on Tacrolimus-Induced Diabetic Rats[J]. Transplant, 2018, 102(4): e137-e146
- [26] Kropit D, Richter OV, Hans Peter Stobernack, et al. Pharmacokinetics and Safety of Letermovir Coadministered With Cyclosporine A or Tacrolimus in Healthy Subjects[J]. Clin Pharmacol Drug Dev, 2018, 7(1): 9-21
- [27] Kumari R, Saha BC, Sinha BP, et al. Tacrolimus versus Cyclosporine-Comparative Evaluation as First line drug in Vernal keratoconjunctivitis[J]. Nepal J Ophthalmol, 2018, 9(2): 128-135
- [28] Poshekhontseva VY, Fokina VV, Sukhodolskaya GV, et al. Effect of Starch Composition on the Biosynthesis of Immunosuppressant Tacrolimus (FK-506) by Streptomyces tsukubaensis VKM Ac-2618D Strain[J]. Appl Biochem Biotechnol, 2019, 55(5): 534-543
- [29] Zhong, Jing, Peng, Lulu, Wang, Bowen, et al. Tacrolimus interacts with voriconazole to reduce the severity of fungal keratitis by suppressing IFN-related inflammatory responses and concomitant FK506 and voriconazole treatment suppresses fungal keratitis[J]. Mol Vis, 2018, 24: 187-200
- [30] 张琳, 刘一平, 陶洋, 等. 白芍总苷联合曲安奈德对口腔扁平苔藓患者的临床疗效及其对血清 TNF- $\alpha$  和 IL-6 水平的影响[J]. 川北医学院学报, 2019, 12(6): 686-689
- [31] Hui-Biao L, Mu-Yuan C, Zhen-Wen Q, et al. Efficacy and safety of Kangfuxin liquid combined with aminosalicic acid for the treatment of ulcerative colitis[J]. Medicine, 2018, 97(21): e10807