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康复新液联合胸腺五肽局部应用对口腔溃疡的疗效及对血清 TNF- α 、IL-6、SOD、SIgA、IgG 的影响 *

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摘要 目的:研究康复新液联合胸腺五肽局部应用对口腔溃疡的疗效及对血清肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白介素-6(Interleukin, IL-6)、超氧化物歧化酶(Superoxide dismutase, SOD)、唾液分泌型免疫球蛋白(secretory immunoglobulin A, SIgA)、免疫球蛋白(immunoglobulin, IgG)的影响。**方法:**选取2014年12月至2016年12月我院收治的86例口腔溃疡患者,按照随机数表法分为康复新液组($n=43$)和联合治疗组($n=43$)。康复新液组患者采取康复新液治疗,联合治疗组则采取康复新液联合胸腺五肽局部应用治疗。观察并比较两组患者临床治疗效果、症状改善情况、疼痛缓解时间和溃疡愈合时间、血清 TNF- α 、IL-6、SOD 水平变化情况、SIgA 和 IgG 水平以及不良反应和复发情况。**结果:**与治疗前比较,两组患者治疗 72 h 后疼痛程度均明显改善,溃疡直径显著缩小,总积分明显下降,总积分下降指数显著攀升($P<0.05$);血清 TNF- α 、IL-6 水平明显下降,血清 SOD 水平明显升高($P<0.05$)。与康复新液组患者相比,联合治疗组患者总有效率明显升高($P<0.05$),疼痛程度、溃疡直径、总积分、总积分下降指数改善情况更优($P<0.05$),缓解时间和溃疡愈合时间明显缩短($P<0.05$),血清 TNF- α 、IL-6 水平下降和血清 SOD 水平升高程度更明显($P<0.05$)。两组患者治疗后 SIgA 水平较治疗前明显升高, IgG 水平较治疗前显著降低,且联合治疗组以上指标的改善情况显著优于康复新液组($P<0.05$),复发率明显较低($P<0.05$)。**结论:**康复新液联合胸腺五肽局部应用治疗口腔溃疡临床治疗效果明显优于康复新液单药治疗,可有效缓解疼痛、减轻患者相关症状、加速愈合,其机制可能与降低血清 TNF- α 、IL-6 水平及提高血清 SOD 水平有关。

关键词:康复新液;胸腺五肽;口腔溃疡;肿瘤坏死因子- α 、白介素-6、超氧化物歧化酶

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Effect of Kangfuxin Liquid Combined with Topical Application of Thymopentin on Oral Ulcer and Serum TNF- α , IL-6, SOD, SIgA and IgG Levels*

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ABSTRACT Objective: To study the effect of Kangfuxin liquid combined with topical application of thymopentin on the oral ulcer and the serum TNF- α , IL-6, SOD, SIgA and IgG levels. **Methods:** 86 cases with oral ulcer from December 2014 to December 2016 were selected and divided into the Kangfuxin Liquid group ($n=39$) and the combination therapy group ($n=39$) according to the random number table. Kangfuxin Liquid group was treated by Kangfuxin Liquid, while combination therapy group was given thymopentin topical on the basis of Kangfuxin Liquid. The clinical effect, improvement of symptoms, relief time of pain and ulcer healing time, serum TNF- α , IL-6, SOD levels, SIgA and IgG levels and the incidence of adverse reactions and relapse were compared between two groups. **Results:** At 72h after treatment, compared with before treatment, the pain levels of both groups were significantly improved, ulcer diameters were significantly reduced, total scores were significantly decreased, the total score drop index were significantly decreased ($P<0.05$). The relief time of pain and ulcer healing time of Kangfuxin Liquid group were longer than those of the combined treatment group ($P<0.05$); the serum TNF- α and IL-6 levels were significantly decreased, serum SOD levels were significantly increased ($P<0.05$). Compared with the Kangfuxin Liquid group, the total effective rate of combined treatment group was significantly higher ($P<0.05$), the improvement of pain level, ulcer diameter, total score and total score drop index were better ($P<0.05$), the levels of serum TNF- α and IL-6 were significantly decreased and the level of serum SOD was significantly increased ($P<0.05$); the SIgA levels in both groups were significantly higher than

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those before treatment, the levels of IgG were significantly decreased than those before treatment, which were improved significantly better in the combined treatment group than those of the Kangfuxin Liquid group ($P<0.05$); The recurrence rate was significantly lower in the combined treatment group ($P<0.05$). **Conclusion:** The combination of Kangfuxin liquid and thymopentin was more effective than Kangfuxin liquid single used in the treatment of oral ulcer, it could effectively relieving the pain and symptoms, accelerat the healing, which might be related to the decrease of serum TNF- α , IL-6 levels and increase of serum SOD levels.

Key words: Kangfuxin liquid; Thymopentin topical; Oral ulcer; TNF- α ; IL-6; SOD

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前言

口腔溃疡又称“口疮”，是一种发生于口腔黏膜的常见溃疡性损伤，常见于舌头、舌腹、唇内侧、前庭沟、软腭、颊粘膜等部位^[1,2]。该病发作时伴有剧烈疼痛且局部有明显灼痛，严重者甚至影响正常说话和进食，同时该病易反复发作，具有自限性^[3,4]。口腔溃疡的发病机制较为复杂，与患者内分泌、免疫、细菌感染、营养缺乏、精神压力、消化功能紊乱等因素均有一定关系^[5,6]。近年来研究显示口腔溃疡的发生发展与多种细胞因子相关，患者血清 TNF- α 、IL-6 以及 SOD 水平存在改变^[7]，故在治疗过程中可通过严密监测上述细胞因子水平变化评估疾病的进展情况。有研究表明康复新液治疗口腔溃疡疗效确切，胸腺五肽局部应用治疗则止痛迅速，加速愈合，两者联合用药疗效甚佳^[8]。但关于两者联合用药治疗的作用机制却报道鲜少。因此，本研究应用康复新液联合胸腺五肽局部应用治疗口腔溃疡，进一步探究了其临床疗效以及对血清 TNF- α 、IL-6 以及 SOD 水平的影响，现报道如下。

1 资料与方法

1.1 资料

选取 2014 年 12 月至 2016 年 12 月我院收治的 86 例口腔溃疡患者，按照随机数表法分为康复新液组($n=43$)和联合治疗组($n=43$)。康复新液组中，男性 29 例，女性 14 例，年龄 17~68 岁，平均年龄(35.6 ± 6.3)岁；病程 0.7~12 年，平均病程(4.1 ± 1.5)年。联合治疗组中，男性 32 例，女性 11 例，年龄 18~69 岁，平均年龄(37.4 ± 3.7)岁；病程 0.8~13 年，平均病程(4.7 ± 1.9)年。纳入标准：(1)符合《口腔黏膜病学》中关于口腔溃疡的诊断标准^[9]者；(2)有口腔黏膜溃疡、糜烂以及疼痛史者；(3)口腔溃疡反复发作且病程 ≥ 6 个月者；(4)本次发病 <72 h 者；(5)对整个研究知情同意且签署相关同意书者。排除标准：(1)合并严重白塞病、口腔溃疡者；(2)合并严重全身系统性疾病者；(3)合并肿瘤者；(4)于研究前 30 d 内接受过相关药物治疗者；(5)对本研究药物过敏者。整个研究经我院伦理委员会批准后实施。两组患者在病程、性别等临床资料的比较差异无统计学意义，具有可比性($P>0.05$)。

1.2 治疗方法

康复新液组患者采取康复新液(生产厂商：四川好医生攀西药业有限责任公司，生产批号：20140728，规格：100 mL)治疗。每日 4 次，每次 10 mL 吞服，用药后 1 h 内禁水、禁食。联合治疗组则采取康复新液联合胸腺五肽冻干粉(生产厂商：海南中和药业有限公司，生产批号：20131218，规格：10 mg)局部应

用治疗。康复新液用药剂量同康复新液组，胸腺五肽冻干粉每日 2 次，每次 2 mg，局部涂擦，每 3 d 复诊 1 次。

1.3 观察指标

观察并比较两组患者临床治疗效果、症状改善情况、疼痛缓解时间和溃疡愈合时间、血清 TNF- α 、IL-6、SOD 水平变化情况、SIgA 和 IgG 水平，并在治疗过程中详细记录患者发生不良反应情况。

症状改善情况：包含总积分、疼痛程度、溃疡直径、总积分下降指数。患者疼痛程度采用主观疼痛^[10]进行评定：毫无疼痛为 0 分；轻度疼痛为 1 分；中度疼痛为 2 分，疼痛难忍为 3 分。溃疡直径采用标尺进行测量，测量后根据直径长度进行评分：0 分：溃疡直径 <1 mm；1 分：溃疡直径 <4 mm；2 分：4 mm $<$ 溃疡直径 <8 mm；3 分：溃疡直径 >8 mm。总积分：0~6 分，为疼痛程度和溃疡直径之和。总积分下降指数=(治疗前-治疗后)/治疗前 $\times 100\%$ 。

炎症因子：于治疗前 1 d 和治疗 1 周后清晨空腹采集患者静脉血 5 mL，离心(时间：10 min，转速：3000 r/min，半径：3 cm)分离血清后用于检测 TNF- α 、IL-6、SOD、IgG 以及 SIgA 水平。TNF- α 、IL-6 以及 SOD 水平检测均应用酶联免疫法进行检测，SIgA 和 IgG 水平检测则采用放射免疫法进行检测，其检测仪器为贝克曼库尔特 UniCel DxI 800 型全自动化学发光免疫分析仪，酶联免疫法检测试剂盒购自上海沪宇生物科技有限公司，操作严格按照试剂盒说明书进行。

1.4 疗效评定标准

痊愈：治疗后 72 h 内疼痛完全消失，口腔溃疡基本愈合；好转：治疗后 72 h 内疼痛明显改善，口腔溃疡面积缩小显著；无效：治疗后 72 h 内疼痛和口腔溃疡面积无明显变化，其愈合时间和疼痛消失时间均在 5 d 以上^[11]。

1.5 统计学分析

本次实验数据处理选择 SPSS11.5 软件包进行，计量资料采取($\bar{x} \pm s$)来表示，对计量资料进行 t 检验，计数资料以[n(%)]表示，对计数资料采用 χ^2 检验进行比较，以 $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组患者临床治疗效果比较

治疗 72 h 后，联合治疗组患者总有效率达到 95.35%，而康复新液组患者总有效率仅为 74.42%，两组比较差异具有统计学意义($P<0.05$)，见表 1。

2.2 两组患者临床症状改善情况比较

治疗前，两组患者总积分、疼痛程度以及溃疡直径比较差

异均无统计学意义($P>0.05$);治疗 72h 后,患者疼痛程度均明显 著攀升,且联合治疗组患者改善程度显著优于康复新液组患者改善,溃疡直径显著缩小,总积分下降明显,总积分下降指数显 ($P<0.05$),见表 2。

表 1 两组患者临床治疗效果比较[n(%)]

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

Groups	n	Cure	Improved	Invalid	Total effective rate
Kangfuxin Liquid group	43	15	17	11	74.42
Combination therapy group	43	23	18	2	95.35 ^Δ

Note: Compared with Kangfuxin Liquid group, ^Δ $P<0.05$.

表 2 两组患者临床症状改善情况比较($\bar{x} \pm s$)Table 2 Comparison of the improvement of clinical symptoms between two groups($\bar{x} \pm s$)

Groups	n	Time	Pain level(分)	Ulcer diameter (mm)	Total points(分)	Total score drop index(%)
Kangfuxin Liquid group	43	Before treatment	2.69 $\pm$ 0.74	2.55 $\pm$ 0.82	4.67 $\pm$ 0.98	
		After treatment	1.37 $\pm$ 0.32 ^Δ	1.64 $\pm$ 0.38 ^Δ	3.25 $\pm$ 0.96 ^Δ	54.55 $\pm$ 9.17
Combination therapy group	43	Before treatment	2.58 $\pm$ 0.43	2.49 $\pm$ 0.69	4.58 $\pm$ 0.94	
		After treatment	0.68 $\pm$ 0.25 ^{ΔΔ}	0.89 $\pm$ 0.25 ^{ΔΔ}	2.12 $\pm$ 0.87 ^{ΔΔ}	86.12 $\pm$ 11.28 ^Δ

Note: Compared with Kangfuxin Liquid group, ^Δ $P<0.05$; Compared with before treatment, ^{ΔΔ} $P<0.05$.

2.3 两组患者疼痛缓解时间和溃疡愈合时间比较 合治疗组更长,差异具有统计学意义($P<0.05$),见表 3。

治疗后,康复新液组疼痛缓解时间和溃疡愈合时间均较联

表 3 两组患者疼痛缓解时间和溃疡愈合时间比较($\bar{x} \pm s, d$)Table 3 Comparison of the Pain relief time and Ulcer healing time between two groups($\bar{x} \pm s, d$)

Groups	n	Pain relief time	Ulcer healing time
Kangfuxin Liquid group	43	3.64 $\pm$ 0.73	4.82 $\pm$ 1.19
Combination therapy group	43	2.78 $\pm$ 0.49 ^Δ	3.17 $\pm$ 0.58 ^Δ

Note: Compared with Kangfuxin Liquid group, ^Δ $P<0.05$.

2.4 两组患者治疗前后血清 TNF- α 、IL-6、SOD 水平比较 较治疗前明显下降,而血清 SOD 水平则明显升高,且与康复新

液组相比,联合治疗组改善水平更优($P<0.05$),见表 3。
治疗前,两组患者血清 TNF- α 、IL-6、SOD 水平比较差异无
统计学意义($P>0.05$);治疗 72 h 后,两组血清 TNF- α 、IL-6 水平

表 4 两组患者治疗前后血清 TNF- α 、IL-6、SOD 水平比较($\bar{x} \pm s$)Table 4 Comparison of the serum TNF- α , IL-6 and SOD levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Time	TNF- α (μ g/L)	IL-6(ng/mL)	SOD(U/L)
Kangfuxin Liquid group	43	Before treatment	46.34 $\pm$ 15.28	159.38 $\pm$ 17.29	237.26 $\pm$ 36.48
		After treatment	39.24 $\pm$ 13.21 ^Δ	105.34 $\pm$ 13.56 ^Δ	247.48 $\pm$ 35.71 ^Δ
Combination therapy group	43	Before treatment	46.29 $\pm$ 12.78	156.23 $\pm$ 16.92	240.89 $\pm$ 34.78
		After treatment	28.21 $\pm$ 9.96 ^{ΔΔ}	74.29 $\pm$ 7.98 ^{ΔΔ}	296.37 $\pm$ 39.45 ^{ΔΔ}

Note: Compared with Kangfuxin Liquid group, ^Δ $P<0.05$; Compared with before treatment, ^{ΔΔ} $P<0.05$.

2.5 两组患者治疗前后 SIgA 和 IgG 水平比较 高,IgG 水平较治疗前显著降低,且联合治疗组患者相关水平

改善情况显著优于康复新液组患者($P<0.05$),见表 5。
治疗前,两组患者 SIgA 和 IgG 水平比较差别无明显统计
学意义($P>0.05$);治疗后,两组患者 SIgA 水平较治疗前明显升

表 5 两组患者治疗前后 SIgA 和 IgG 水平比较($\bar{x} \pm s$)Table 5 Comparison of the SIgA and IgG levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Time	SIgA(mg/dL)	IgG(mg/L)
Kangfuxin Liquid group	43	Before treatment	34.97 $\pm$ 8.82	47.99 $\pm$ 8.81
		After treatment	51.85 $\pm$ 10.43 ^Δ	36.13 $\pm$ 7.59 ^Δ
Combination therapy group	43	Before treatment	34.96 $\pm$ 8.84	48.12 $\pm$ 8.73
		After treatment	64.81 $\pm$ 11.34 ^{ΔΔ}	23.56 $\pm$ 6.61 ^{ΔΔ}

Note: Compared with Kangfuxin Liquid group, ^Δ $P<0.05$; Compared with before treatment, ^{ΔΔ} $P<0.05$.

2.6 两组患者不良反应和复发情况比较

治疗过程中以及治疗 72h 后,所有患者均未出现任何严重不良反应。而在随后随访患者 6 个月期间,康复新液组发生复发 15 例,联合治疗组仅发生 6 例,联合治疗组复发率(13.95%)显著低于康复新液组(34.88%)($P<0.05$)。

3 讨论

口腔溃疡是一种口腔黏膜非特异性的炎症反应,其特征为急性炎症性溃疡,临床表现为口腔黏膜糜烂、疼痛、红肿、坏死等。随着病情的发展,严重者并发感染,病情反复长达数年,诊治不愈,严重影响患者日常说话、饮水、进食。中医认为口腔溃疡的发生多与内伤情志、外伤六淫后致使脏腑功能失调有关^[12]。中医学中也有“心气通于舌”,“舌为脾之外候”,“脾开窍于口”等之说。有学者认为虽然口腔溃疡病位在于口舌,但其发病机制却关乎患者心脏脾三重要脏器的功能失调^[13]。西医则认为口腔溃疡的发病机制虽然较为复杂,但其与患者细菌感染、营养缺乏、精神压力、免疫功能减退、消化功能紊乱等因素均有一定关系^[14]。

目前,临床治疗该病多采用止痛、抗菌、消炎以及激素类药物进行治疗,但首要还是以中药治疗为主。康复新液是由美洲一种大蠼干燥虫体中的乙醇提取物而制成的溶液,主要成分有黏糖氨酸、肽类、多元醇、促生长因子以及多种氨基酸^[15]。其中,黏糖氨酸可有效增强机体细胞免疫功能,并促进自由基的释放来达到杀菌的作用;同时还能通过分泌白三烯、前列腺素等调节炎症反应,加速机体组织再生。肽类、多元醇以及多种氨基酸可促进创面胶原蛋白合成,改善组织微循环,达到创面快速愈合的目的。同时,康复新液还能提高血清溶菌酶以及淋巴细胞的活性,有效调节体内 SOD 水平。而胸腺五肽作为一种免疫调节剂,可双向调节患者机体免疫功能,进一步使患者免疫反应趋于正常,可有效提高临床疗效^[16,17]。有文献显示,将胸腺五肽注射用药治疗口腔溃疡,疗效欠佳,但将其局部应用涂擦于创面的疗效甚好^[18]。此外,也有文献表明,将胸腺五肽联合康复新液治疗口腔溃疡,其疗效优于单独应用康复新液治疗^[19]。本研究中,联合治疗组临床总有效率更高,随访 6 个月内的复发率更低,提示其疗效优于单用康复新液治疗。

TNF- α 、IL-6、SOD 为机体炎症反应的重要介质。本研究中,患者入院后对其 TNF- α 、IL-6 水平显著升高,SOD 水平明显降低,说明口腔溃疡的发生发展与细胞因子有一定关系,因为患者机体 TNF- α 、IL-6 以及 SOD 水平存在表达改变,这与相关研究结果无异^[20]。本研究结果也表明患者在治疗后血清 SOD 水平显著升高,该水平由于直接反应机体抗氧化能力,其升高说明联合用药治疗可有效增强机体抗氧化能力,进而增强机体免疫力。此外,本研究结果还显示患者治疗后血清 TNF- α 、IL-6 水平出现显著下降,表明联合用药治疗后患者炎症反应得到一定控制,因此康复新液和胸腺五肽联合治疗可有效抑制机体炎症反应,减轻疼痛,加速愈合。

SigA 属于一种局部抗菌免疫球蛋白,其水平与病原菌密切相关,当病原菌侵入时,其水平显著下降,因此检测并观察其水平可以有效反应口腔的感染情况;而 IgG 水平则是在口腔黏膜出现受损时渗入口腔中,致使唾液中相关水平明显升高。因

此,二者均能有效反映机体免疫功能,且与溃疡愈合时间有一定关系。本研究中,两组患者 SigA 水平较治疗前明显升高,IgG 水平较治疗前显著降低,且联合治疗组相关水平改善情况显著优于康复新液组,证实联合治疗可有效改善患者机体免疫功能。同时,患者治疗后临床症状得到明显改善,有效缩短其疼痛时间和溃疡愈合时间,说明联合治疗在改善 SigA 和 IgG 水平的同时,对患者愈合时间也有一定改善,证实 SigA 和 IgG 水平与愈合时间有一定关系。

总之,康复新液联合胸腺五肽局部应用治疗口腔溃疡临床治疗效果佳,可有效缓解疼痛、减轻患者相关症状、加速愈合,其作用机制可能与提高血清 SOD 水平,降低血清 TNF- α 、IL-6 水平有关。

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