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全蝎软膏联用积雪苷软膏治疗增生性瘢痕的效果评价*

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摘要 目的:观察全蝎软膏联用积雪苷软膏在早期治疗增生性瘢痕的治疗效果,并进一步探讨对组织中 TGF- β 信号通路的影响。**方法:**选取新西兰大白兔建立兔耳增生性瘢痕模型,随机平均分为对照组、模型组、全蝎软膏组、积雪苷软膏组和联合用药组;术后立即在治疗组患处涂抹全蝎软膏和/或积雪苷软膏,空白组和模型组涂抹 PBS 处理,连续用药 35 天并拍照记录各组瘢痕的治疗情况;于术后 35 d 收集各组兔耳组织样本进行病理检测、荧光定量 PCR 和 western blot 检测。**结果:**模型组于术后 35 天可见明显增生性瘢痕,各治疗组中联合用药组比单独药物治疗组的抑制效果更为显著,经治疗后无增生性瘢痕出现。H.E 染色结果显示,与模型组相比,各治疗组经治疗后组织纤维化程度均减轻,胶原蛋白量均有不同程度降低,但联合用药可显著改善组织纤维化程度。荧光定量 PCR 和 western blot 检测结果表明,与模型组相比,治疗组组织内的 MMP 水平均呈上升趋势,Ⅰ型胶原蛋白(Col I)、Ⅲ型胶原蛋白(Col III)及 Samd 4 蛋白水平均不同程度下降,联合用药组差异最为显著,治疗效果优于单独用药组。**结论:**全蝎软膏联用积雪苷软膏可有效改善组织内细胞纤维化水平并减少胶原蛋白的沉积,可通过 Smad 4 蛋白的表达量调控 TGF- β 信号通路而抑制增生性瘢痕的形成。

关键词:全蝎软膏;积雪苷软膏;增生性瘢痕;胶原蛋白;TGF- β 信号通路

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Evaluation of the Effect of Scorpion Ointment Combined with Asiaticoside Ointment in the Treatment of Hypertrophic Scar*

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ABSTRACT Objective: To observe the early effect of scorpion ointment combined with asiaticoside ointment on hypertrophic scar and the effect of TGF- β signaling pathway in tissues was further explored. **Methods:** The New Zealand white rabbits were randomly divided into control group, model group, scorpion ointment group, asiaticoside ointment group and combined drug group. Scorpion ointment and/or asiaticoside ointment were applied immediately after operation in the treatment group for 35 consecutive days, and the treatment of scars in each group was recorded by photography. Pathological examination, real-time PCR and Western blot were performed on rabbit ear tissue samples of each group 35 days after operation. **Results:** Typical hypertrophic scars were observed in model group 35 days after operation and the inhibitory effect of combined drug treatment group was more significant than that of single drug treatment group. The results of H. E staining showed that compared with the model group, the degree of tissue fibrosis and the amount of collagen in each treatment group were reduced to some extent after treatment, but the combined use of drugs could significantly improve the degree of tissue fibrosis. The results of real-time PCR and western blot showed that the MMP level in the treated group was higher than that in the model group, and the levels of type I collagen (Col I), type III collagen (Col III) and Samd 4 protein. The differences were all different, and the difference in the combination group was the most significant, and the treatment effect was better than that in the single drug group. **Conclusion:** The combination of scorpion ointment and asiaticoside ointment can effectively improve the level of cell fibrosis and reduce the deposition of collagen. The expression of Smad 4 protein can regulate the TGF- β signaling pathway and inhibit the formation of hypertrophic scar.

Key words: Scorpion ointment; Asiaticoside ointment; Hypertrophic scar; Collagen protein; TGF- β signaling pathway

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前言

增生性瘢痕(hypertrophic scar, HTS)作为一种临床上常见的皮肤疾病,以皮肤损伤后机体不能进行正常的创面修复而致使愈合后瘢痕继续增殖形成病理性增生为特点;发病时局部皮肤常伴有瘙痒、疼痛或灼热等症状,偶发于关节时可对关节活动造成障碍,常给患者的心理和身体造成双重影响^[1-3]。目前关于 HTS 具体的发病机制尚不明确,我国传统医学认为金刀所伤、水火烫伤所致的“气滞血瘀”为发病根本,“邪毒内侵、余毒未散”为其发病的表征^[4-6]。现代分子医学研究证明,HTS 的形成主要由成纤维细胞(fibroblast, FB)过量增殖、胶原蛋白在细胞外基质(extracellular matrix, ECM)内过量表达并沉积引起。其中,转化生长因子- β (transforming growth factor- β , TGF- β)被认为是影响创面愈合及增生性瘢痕形成的重要因素,可通过调节 TGF- β /Smad 分子信号通路和控制基质金属蛋白酶(Matrix metalloproteinases, MMP)的合成影响胶原纤维的合成与沉积。这是近年来研究瘢痕发病机制的热点方向^[7-9]。

目前,临床上常用治疗 HTS 的方法包括外科手术、药物治疗、加压、放疗和激光治疗等,有时也采取几种方法联用的综合疗法,虽取得较好的治疗效果,但仍存在治疗周期长、复发率高以及副作用大等缺点^[10-12]。祖国医学中在预防及治疗增生性瘢痕方面积累了丰富的经验,对比西医的治疗方式,中草药制剂不仅具有副作用小、不易复发等优点,可以在发病早期预防 HTS 的形成^[13]。积雪苷具有清热解毒之功效,具有镇痛、抗纤维化和促进伤口愈合等功效,可抑制 HTS 的形成^[14-16];全蝎软膏具有抗菌消炎、止痛止痒、增强创伤皮肤代谢等作用,已在疾病治疗方面取得了良好应用效果^[17,18]。

本研究通过建立兔耳增生性瘢痕模型,拟将全蝎软膏和积雪苷软膏联用进行 HTS 的治疗,通过苏木精-伊红染色(H.E)法、荧光定量 PCR(real-time PCR)法及免疫印迹(Western-blot)法对治疗效果进行综合评价,以期为临床治疗 HTS 疾病提供新途径。

1 材料与方法

1.1 材料

1.1.1 药品及主要试剂 全蝎软膏由黑龙江中医药大学附属二院提供;积雪苷霜软膏购自海南普利制药股份有限公司(国药准字 Z46020054);苏木精-伊红染色液、PBS 磷酸盐缓冲液、多聚甲醛购自 Sigma-Aldrich(上海)贸易有限公司;反转录试剂盒、SYBR qPCR Mix 试剂盒购自宝生物工程(大连)有限公司;兔抗人 Smad 4 单克隆抗体、兔抗人 GAPDH 单克隆抗体购自武汉菲恩生物科技有限公司;HRP 标记羊抗兔二抗购自北京中杉金桥生物技术有限公司。

1.1.2 主要仪器 Real-time PCR 仪(CFX96)购自伯乐生命医学产品(上海)有限公司;显微镜(DM 2000)购自奥林巴斯株式会社;酶标仪(Multiskan FC)、低温离心机、电子天平、western blot 检测分析仪购自赛默飞世尔科技(中国)有限公司;超微量分光光度计(K5600)购自上海昂拉仪器有限公司。

1.1.3 实验动物 清洁级新西兰大白兔共 20 只,重为 2.5~3.5 Kg,购自辽宁长生生物技术股份有限公司(许可证编号:SCXK 辽 2015-0001)。饲养于黑中医附属二院的动物中心内,购买后适应性饲养 7~10 天,环境条件为 25 $\pm$ 1 $^{\circ}$ C、湿度 55%~65%、饮食及进水均自由。

1.2 方法

1.2.1 兔耳增生性瘢痕模型的建立及给药 将 20 只新西兰大白兔分随机平均分成 5 组,每组 4 只,命名为:空白组、模型组、积雪苷软膏组、全蝎软膏组和联合用药组;采用 Uzun. H 等人^[19]建立方法进行了 HTS 造模术。主要步骤:用 20% 乌拉坦剂量为 5.0 mL/Kg 耳缘静脉注射,麻醉后使用 75%酒精对兔耳部皮肤进行经消毒,在左右耳沿中线两侧分别作 6 个直径为 8 mm 的圆形皮肤缺损创面,切除兔耳全层皮肤、刮除软骨膜并保留软骨,出血点以压迫止血,每两个创面之间间隔 1 cm;造模术后随使用积雪苷软膏和全蝎软膏对患处进行连续涂抹治疗 35 天,数码相机记录兔耳瘢痕形态变化。具体治疗方案见表 1。

表 1 兔耳增生性瘢痕的治疗方案

Table 1 Treatment plan for rabbit ear hypertrophic scar

Groups	Therapeutic modalities	Administered dose	Treatment time
Control	-	-	35 d
Model	PBS	0.4 mL/d	35 d
Asiaticoside ointment	Asiaticoside ointment	0.4 mL/d	35 d
Scorpion ointment	Scorpion ointment	0.4 mL/d	35 d
Hybrid Group	Asiaticoside ointment+ Scorpion ointment	Asiaticoside ointment 0.2 mL/d+ Scorpion ointment 0.2 mL/d	35 d

1.2.2 动物样本的采集与处理 于用药后的第 35 天分别在无菌条件下切取药物治疗组、空白组及模型组对应部位的兔耳瘢痕组织皮肤,一部分用 10%的甲醛溶液进行固定,石蜡包埋后留作 H.E 染色试验;另一部分组织样本用 PBS(0.01 M, pH=7.4)冲洗后保存到 -80 $^{\circ}$ C 冰箱中备用,用于 real-time PCR 和 western blot 检测。

1.2.3 H.E 染色 将上述经石蜡包埋的病理组织和正常组织切成厚度约为 5 μ m 的切片,置于经多聚赖氨酸附膜的载玻片上 65 $^{\circ}$ C 作用 4 小时;按照苏木素-伊红(H.E)染色液说明书进行操作,分别经苏木精染液 5 min、反蓝液蓝化 5 min、伊红染色液 30 s,风干后用中性树脂胶封片并烤干,显微镜下观察并记录结果。

1.2.4 Real-time PCR 法检测胶原蛋白及 MMP mRNA 的表达 分别取各组组织约 0.5 g 放入 EP 管中,按照 Trizol 总 RNA 提取试剂盒说明书提取组织内 RNA,取 1 μ L 提取液于蛋白分析仪测定含量及纯度;按照反转录试剂盒说明书所述配置总反应为 10 μ L 反转录体系,置于 PCR 以上按 37 $^{\circ}$ C 15 min, 98 $^{\circ}$ C 5 min, 4 $^{\circ}$ C 30 min 程序进行反转录,反应后将 cDNA 定量

至 100 ng/ μ L。随后,配置总体积为 20 μ L 的 real-time PCR 反应体系:SYBR qPCR Mix 10 μ L,上游/下游引物各 1 μ L,DEPC 水 7 μ L,cDNA 1 μ L;反应条件如下:95 $^{\circ}$ C 3 min 预变性,95 $^{\circ}$ C 10 s,95 $^{\circ}$ C 5 s,60 $^{\circ}$ C 30 s,共 40 个循环并于 60 $^{\circ}$ C 下充分延伸 10 min,real-time PCR 引物见表 2,反应结束后导出并整理数据。

表 2 real-time PCR 扩增引物

Table 2 The amplification primers of real-time PCR

	Primers name	Primers sequence (5'-3')	Size (bp)
Actin	Actin-F	GACAAAGTGTGGTGGGAATG	21
	Actin-R	GGAGTGATGCCAGATCTTCTC	21
MMP	MMP-F	CAGATGCTGAAACCCTGAAGA	21
	MMP-R	CTTGACAGGTCTGGTGTGTAAT	22
Col I	Col I-F	GGCAACAGCAGGTTCACCTTA	20
	Col I-R	GGGCAAACGAGATGGCTTAT	20
Col III	Col III-F	CTCCCAGAACATCACCTATCAC	22
	Col III-R	TCAGCTTCAGGGCTTCTTTA	21

1.2.5 Smad 4 蛋白的 western blot 检测 将 1.2.2 中所述的正常组织和瘢痕组织剪碎并与一定体积的 PBS 置于玻璃匀浆器中,低温下充分研磨,将匀浆于 10 000 r/min 离心 5 min 取上清液,考马斯亮蓝法对测定提取的上清液中蛋白浓度,取 20 μ L 上清液经 SDS-PAGE 凝胶电泳作用后电转至 PVDF 膜上;同时,设定甘油醛-3-磷酸脱氢酶(GAPDH)蛋白为内参分别经 Smad 4 单克隆抗体及 1:2 000 HRP 标记羊抗兔二抗孵育,经 ECL 发光显色条带并将结果使用 western blot 图像分析系统处理。

1.2.6 统计学处理 使用 Spss 13.0 软件进行分析,以 $\bar{x} \pm s$ 表示,采用单因素方差分析加两两多重比较, $P < 0.05$ 表示有统计学差异。

2 结果

2.1 外观形态特征观察

术后分别在 3 个治疗组的兔耳患处直接涂抹积雪苷软膏和/或全蝎软膏连续用药 35 d,与对照组和模型组相比(图 1A 和 B),联用组的治疗效果最显著,可于治疗后的第 25 d 后无增生性瘢痕出现(图 1E),全蝎软膏组次之,与治疗后的第 35 d 无增生性瘢痕出现(图 1D),而积雪苷软膏治疗后的皮肤表面虽愈合速度较快,但会出现质地较柔软且较小的瘢痕(图 1C)。

2.2 H.E 染色结果

H.E 染色结果表明:模型组于 35 d 时增生性瘢痕组织在显微镜下观察可见有大量的成纤维细胞和胶原纤维聚集,且真皮层增厚伴随毛细血管炎症细胞浸润;在三个治疗组中,全蝎软膏联用积雪苷软膏组连续治疗 35 d 后,组织内成纤维细胞数量显著减少且无明显炎性细胞浸润出现;而全蝎软膏组和积雪苷软膏组的治疗效果较显著,组织内有少量的成纤维细胞聚集并伴随轻微的炎性细胞浸润。(见图 2)

2.3 组织内胶原蛋白及 MMP mRNA 的检测结果

荧光定量 PCR 扩增结果如图 3 所示,与空白组和模型组相比,经全蝎软膏和/或积雪苷软膏连续治疗的 3 组中,组织内的 MMP 含量均有不同程度的升高,其中联合用药组 MMP 上升最显著($P < 0.05$);而联用组中 Col I 型胶原蛋白、Col III 型胶原蛋白的表达量与其他各组相比显著降低($P < 0.01$),表明 MMP 的大量合成能够抑制 FB 的表达,进而抑制了胶原蛋白的沉积以阻止瘢痕的形成。

2.4 兔耳增生性瘢痕组织中 Smad 4 蛋白的检测结果

对各实验组组织中 Smad 4 蛋白进行 western blot 检测,检测结果如图 4 所示,与空白对照组相比,模型组瘢痕组织中 Smad 4 蛋白量表达水平显著上升,而 3 个治疗组的瘢痕组织中 Smad 4 蛋白水平较模型组均有不同程度的降低($P < 0.05$)。通过图像软件分析后可见,联合用药组和全蝎软膏组的组织中的 Smad 4 蛋白含量与空白对照组较为接近,并且低于积雪苷软膏组,提示全蝎软膏联用积雪苷软膏可以显著抑制瘢痕生长并通过降低 Smad 4 蛋白的表达水平,影响 TGF- β 信号通路的转导,而同剂量全蝎软膏的药效要高于积雪苷软膏。

3 讨论与结论

目前,临床上对增生性瘢痕的治疗方法众多,其中,曲安奈德作为临床上治疗 HTS 常用的糖皮质激素,可通过抑制成纤维细胞增殖及促进胶原降解,并抑制 TGF- β 的表达,是公认的治疗 HTS 的有效药物之一,但用量过大、注射过浅或超过瘢痕组织范围均易使皮肤萎缩、破溃或坏死,不适合用于 HTS 治疗的长期给药^[20]。此外,超声导入联合药物治疗也在 HTS 的治疗上取得了良好的临床效果,但该疗法治疗时间长、且需要监控弹力套的压力,限制了在临床上的使用^[21,22]。经研究表明,积雪苷软膏中的活性物质积雪草具有镇痛消炎、促进伤口愈合及易吸收等特点,对患 HTS 时间为 1~3 月以内的治疗效果显著(87.5%~93.75%);而全蝎软膏的主要成分为全蝎、蜈蚣及冰片

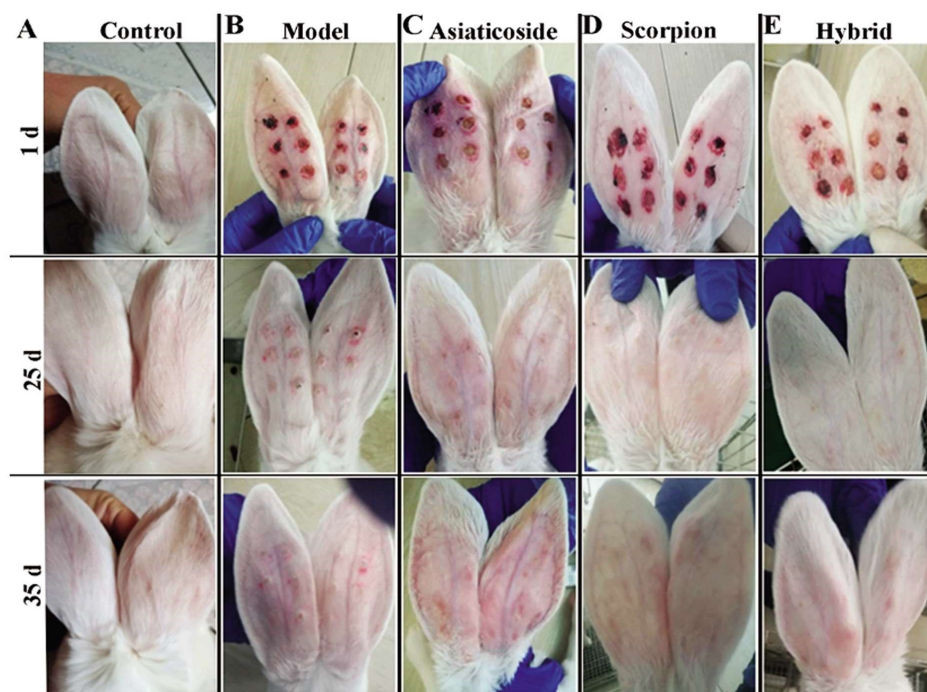


图 1 术后 35 天各组瘢痕组织对比情况

Fig.1 Comparison of scar tissue in each group 35 days after operation

A-E: Observation results of control group, model group, asiaticoside group, scorpion group and hybrid group in 1d, 20 d and 35 d, respectively.

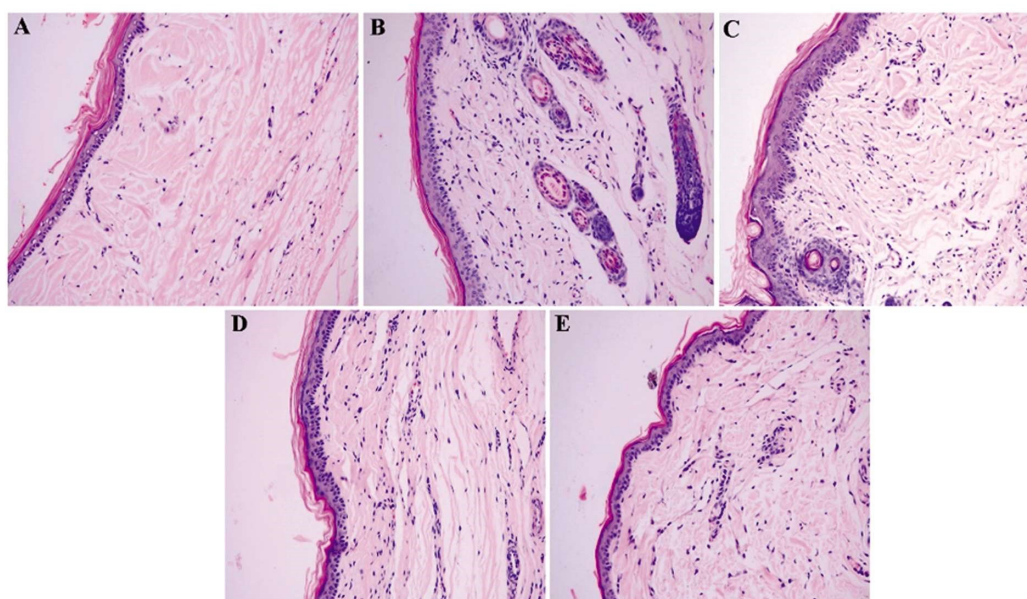


图 2 H.E 染色结果(× 200)

Fig.2 The result of H.E staining. A: control group; B: model group; C: asiaticoside group; D: scorpion group; E: hybrid group. (× 200)

等,具有清热解毒、祛腐生肌之功效,已成功用于多种临床皮肤疾病的治疗之中^[23,24]。本研究选择家兔作为增生性瘢痕模型主要是因为家兔可以较为相似地模拟人类增生性瘢痕,且饲养管理较为方便,可降低实验成本^[25];选择积雪苷软膏与全蝎软膏联用是基于这两种软膏同时具有易吸收的特点,在患处涂抹后可在短时间内吸收进入皮肤组织发挥药效。经造模术后,直接将药物涂抹于兔耳患处,大体形态学观察结果表明,联合用药组可在术后 25 天左右治愈,皮肤表面无瘢痕出现,可恢复至术前水平,较全蝎软膏组和积雪苷软膏组单独治疗效果明显。研

究结果表明,全蝎软膏联合积雪苷软膏对 HTS 的治疗效果较之前报道的积雪苷片联合积雪苷软膏治疗效果更为显著^[26]。江宇峰等^[14]应用积雪苷软膏对构建的兔耳 HTS 进行治疗,H.E 染色结果显示,模型组 HTS 组织纤维化明显,而积雪苷治疗可显著改善纤维化,该结果与本研究所得结果相一致,本研究中的联用组组织内不仅成纤维细胞数量显著减少,且无明显炎症细胞浸润出现,而单独治疗组的组织内伴有少量的成纤维细胞聚集并有轻微的炎症细胞浸润,证实了积雪苷软膏与全蝎软膏联用药更具有治疗优势。

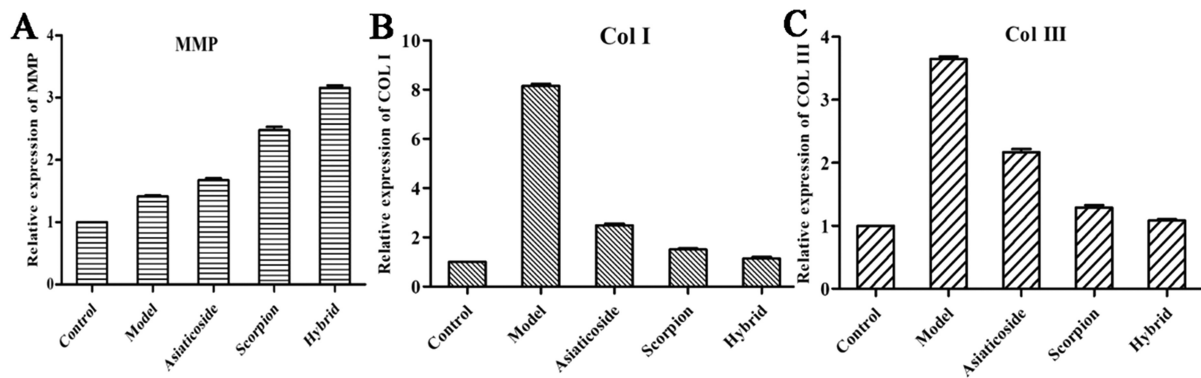


图3 MMP、Col I 及 Col III 的荧光定量 PCR 检测

Fig.3 The detection result of MMP, Col I and Col III by fluorescence quantitative PCR

A: The detection results of MMP; B: The detection results of Col I; C: The detection results of Col III.

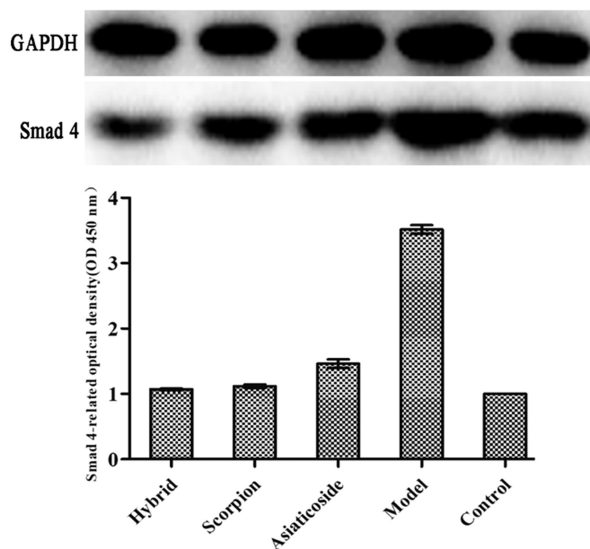


图4 Smad 4 蛋白的 western blot 分析结果

Fig.4 The result of western blot analysis for Smad 4 protein

随着对增生性瘢痕发病机制的不断深入研究,现已在分子和细胞水平上证实了 MAPKs 通路、TGF- β 信号通路等均参与了增生性瘢痕疾病的信号调节,其中,TGF- β -Smads 信号通路被认为是促进/抑制纤维化疾病进程中必不可少的调控通路,TGF- β -MMP 信号通路是调控 I、III 型胶原的信号通路^[27-29]。本研究的荧光定量 PCR 检测结果证实了在治疗组的兔耳增生性瘢痕组织中,MMP 的表达水平较模型组组织含量显著升高,而 I 型胶原、III 型胶原显著降低,证实了 MMPs 可以通过降解细胞外基质(ECM)中的 I 型胶原、III 型胶原而达到抑制瘢痕形成的目的,该结果与 Zhang 等人^[30]此前报道相一致。此外,通过 western blot 及图像软件处理结果可见,模型组中 Smad 4 蛋白水平显著升高,而联用组组织内 Smad 4 蛋白水平与空白对照组水平接近,药物单独治疗组 Smad 4 蛋白水平略有升高,提示在抗增生性瘢痕形成过程中可能与 Smad 4 蛋白的调节有关,可通过调控 TGF- β -Smads 和/或 TGF- β -MMP 信号通路而发挥抗增生性瘢痕作用。

综上所述,本研究采用全蝎软膏联合积雪苷软膏治疗增生性瘢痕效果良好,与单独使用两种药物治疗相比,疗效更好、复发率较低,且能够缩短皮肤愈合时间,这两种药物联用可有效

修复创面,值得在临床上广泛推广与应用。

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