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芩蒿滴鼻液对变应性鼻炎患者鼻分泌物中 SP, TNF- α , Annexin1 及 VCAM-1 含量的影响*

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摘要 目的:探讨芩蒿滴鼻液对变应性鼻炎(AR)患者鼻分泌物中 P 物质(SP)、肿瘤坏死因子- α (TNF- α)、膜联蛋白 1 (Annexin1)、血管细胞黏附分子-1(VCAM-1)含量的影响。**方法:**选取我院耳鼻喉科收治的 AR 患者 92 例,随机分为对照组和实验组两组。对照组 46 例患者予曲安奈德鼻喷雾剂治疗,实验组 46 例患者加用芩蒿滴鼻液治疗。另选取健康体检患者 46 例。采用酶联免疫法测定各组患者鼻分泌物中 TNF- α 、Annexin1 及 VCAM-1 的含量,采用放射免疫法测定 SP 的含量。**结果:**治疗后,两组鼻分泌物中 SP、TNF- α 及 VCAM-1 含量均较治疗前显著下降,Annexin1 含量明显升高($P<0.05$);与对照组比较,实验组鼻分泌物中 SP、TNF- α 及 VCAM-1 含量较低($P<0.05$),Annexin1 含量较高($P<0.05$),实验组临床有效率(91.30%)较对照组(73.91%)显著升高,差异具有统计学意义($P<0.05$)。**结论:**芩蒿滴鼻液能够明显降低 AR 患者鼻分泌物中 SP、TNF- α 、VCAM-1 的含量,上调 Annexin1 的含量。

关键词:芩蒿滴鼻液;变应性鼻炎;P 物质;肿瘤坏死因子- α ;膜联蛋白 1;血管细胞黏附分子-1

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Effect of Scutellaria Artemisia Nasal Drops on the SP, TNF- α , Annexin1 and VCAM-1 Levels in Nasal secretions of Patients with Allergic Rhinitis*

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ABSTRACT Objective: To investigate the effect of Scutellaria Artemisia Nasal Drops on the SP, TNF- α , Annexin1 and VCAM-1 levels in the nasal secretions of patients with allergic rhinitis(AR). **Methods:** 92 cases of patients with AR were selected and randomly divided into two groups. 46 cases in the control group were treated with triamcinolone acetonide spraying agent 20ug/kg, three times a day, sprayed into the nose, 46 cases in the experimental group were treated with Qin Hao nasal drops three times a day 2 weeks for a course of treatment, the TNF- α , Annexin1 and VCAM-1 in nasal secretions were determined by ELISA, SP content of inflammatory mediators was determined by radioimmunoassay. **Results:** After the treatment, the content of SP, TNF- α and VCAM-1 were decreased, the Annexin1 was increased. Compared with the control group, the SP, TNF- α and VCAM-1 levels as well as the clinical efficacy of experimental group were lower ($P<0.05$), the content of Annexin1 of experiment was higher ($P<0.05$). **Conclusion:** Qin Hao nasal drops could significantly reduce the SP, TNF- α , VCAM-1 content and upregulate the Annexin1 content in the nasal secretions of AR patients.

Key words: Qin Hao nasal drops; allergic rhinitis; substance P; tumor necrosis factor alpha; annexin 1; vascular cell adhesion molecule-1

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前言

变应性鼻炎(Allergic Rhinitis, AR)又称过敏性鼻炎,是因为外部环境中过敏原刺激鼻腔粘膜及粘膜下的组织发生变态性反应的疾病^[1,2]。本病多发于青少年人群,我国变应性鼻炎发病率为 10%~25%,并有逐年上升趋势,WHO 已将变应性鼻炎列为 21 世界重点研究和防治的疾病之一^[3]。现代医学多采取组胺类药物为主的抗过敏治疗方法,但并不理想,容易复发,严重影响患者的身体、心理健康,同时也增加经济负担。芩蒿滴鼻液为新疆一支蒿、黄芩、甘草提炼、浓缩而成制剂,对变应性鼻炎的

疗效显著,但对其作用机制至今尚未明确^[4]。本研究通过观察 AR 患者治疗前后鼻分泌物中炎症介质 SP、TNF- α 、Annexin1 及 VCAM-1 含量的变化探究芩蒿滴鼻液对变应性鼻炎的作用机制,现将结果报道如下。

1 资料与方法

1.1 一般资料

选取自 2012 年 1 月至 2014 年 10 月来我院耳鼻喉科收治的变应性鼻炎患者 92 例,患者或家属签订知情同意书,积极配合此次研究,按随机数字表法分组,实验组 46 例,其中男 27

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例,女 19 例,平均年龄 40.6 ± 12.4 岁(25~54);对照组 46 例,其中男 25 例,女 21 例,平均年龄 41.2 ± 11.7 岁(26~54)。健康组 46 例,其中男 24 例,女 22 例,平均年龄 42.3 ± 11.4 岁(27~54),为来我院健康体检者。三组间基本资料具有可比性($P > 0.05$)。

1.2 诊断标准

变应性鼻炎的诊断标准参考临床治疗指南^[5]:① 症状:含有喷嚏、清水样涕、鼻塞、鼻痒两项或两项以上者即可确诊;② 症状每日持续至少 1 个小时;③ 眼部可伴有眼痒、结膜充血;④ 鼻黏膜部位可出现鼻腔水样分泌物,或者出现苍白、水肿等症状;⑤ 变应原皮肤点刺实验阳性,血清特异性 IgE 阳性;⑥ 变应性鼻炎诊断的金标准为鼻激发试验。

1.3 纳入标准

患者符合西医变应性鼻炎的诊断标准;符合中医“鼻鼽”诊断标准;本研究经我院伦理委员会审核通过。排除存在心脑血管、肝、肾及造血功能严重疾病患者;既往有精神性疾病者;精神障碍不能正常交流患者;患有感染性疾病者;存在研究所涉及药物的用药禁忌症者;合并哮喘、荨麻疹等其他变态反应性疾病者;急性鼻炎、嗜酸性粒细胞增多等非变态反应性鼻炎患者;近 3 个月服用使用过类固醇、抗组胺药及缩血管药物患者。

1.4 治疗方法

治疗方法参照国际变应性鼻炎临床治疗指南,对照组予以曲安奈德鼻喷雾剂(南京星银药业集团有限公司,国药准字 H20020360), $20 \mu\text{g/kg}$,每日三次经鼻喷入,2 周为一个疗程,治疗一个疗程;实验组在对照组治疗基础上加用芩蒿滴鼻液(由新疆一支蒿、黄芩经提取浓缩而成,由新疆药物研究所提供,纯度 $> 95\%$) 0.1 g ,2 周为一个疗程,每日三次经鼻滴入,患者均治疗一个疗程。健康组不予以用药。注意事项:治疗期间戒烟戒酒,禁止食用刺激性食物,稳定患者情绪。

1.5 观察指标及检测方法

1.5.1 临床疗效评级标准 诊断标准参照 2010 年《变应性鼻炎诊断和治疗指南》显效:患者临床症状大部分缓解,改善程度大于 1/2 以上;有效:患者临床症状部分缓解,改善程度大于 1/5,小于 1/2;无效:患者临床症状无缓解或加重,改善程度小于 1/5。有效率 = (显效 + 有效) / 总例数 $\times 100\%$ 。

1.5.2 鼻分泌物收集 采用 2 块大小为 $2 \text{ cm} \times 1 \text{ cm} \times 0.1 \text{ cm}$ 含有 200 KIV 抑肽酶的棉块,在治疗前后分别置于双侧鼻腔内,10 min 后取出,放入试管中, 4°C ,2000 r/min 离心 10min 后,去上清液,得 1~3 mL 无黏液和沉渣的鼻分泌物。

1.5.3 标本指标物质定量测定 选用 TNF- α Elisa 试剂盒(上海基免实业有限公司)、VCAM-1 Elisa 试剂盒(上海彩佑实业有限公司)、Annexin1 Elisa 试剂盒(郑州安赛生物科技),利用全自动酶联免疫分析仪(M215175,北京中西远大科技有限公司),通过双抗体夹心酶联免疫吸附法(ELISA),测定鼻分泌物中 TNF- α 、VCAM-1、Annexin1 含量;利用 γ 放射免疫计数器(M368728,北京中西远大科技有限公司),通过放射免疫法测定鼻分泌物中 SP 含量。

1.6 统计学方法

所有统计数据均统一整理,采用 SPSS 17.0 软件包进行分析,符合正态性的计量资料采用均数 $\pm$ 标准差表示,组内状况对比予以配对样本 t 检验,组间比较采用非配对 t 检验, $YIP < 0.05$ 为差异具有统计学意义。

2 结果

2.1 各组鼻分泌物中 SP 含量比较

治疗后,实验组和对照组鼻分泌物中 SP 物质的含量均较治疗前显著下降($P < 0.05$),与对照组比较,实验组治疗后鼻分泌物中 SP 物质含量较低,差异有统计学意义($P < 0.05$);治疗后,实验组 SP 含量与健康组相比差异无统计学意义($P > 0.05$)。见表 1。

表 1 各组患者治疗前后鼻分泌物中 SP 含量比较($\bar{x} \pm s$)

Table 1 Comparison of the SP level in nasal secretions between different groups($\bar{x} \pm s$)

Groups	n	Time	SP(ng/L)
Experimental group	46	Before treatment	52.35 ± 7.47
		After treatment	$43.35 \pm 5.58^{**}$
Control group	46	Before treatment	52.26 ± 7.35
		After treatment	$49.35 \pm 5.08^{**}$
Healthy group	46	-	43.16 ± 5.34

Note: Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{*}P < 0.05$. Compared with the healthy group, $^{\Delta}P < 0.05$.

2.2 各组患者鼻分泌物中 TNF- α 含量比较

治疗后,实验组和对照组鼻分泌物中 TNF- α 的含量均较治疗前显著下降($P < 0.05$),与对照组比较,实验组治疗后鼻分泌物中 TNF- α 含量明显较低,差异有统计学意义($P < 0.05$);治疗后,实验组 TNF- α 含量与健康组相比差异无统计学意义($P > 0.05$)。见表 2。

2.3 各组患者鼻分泌物中 Annexin1 含量比较

治疗后,实验组和对照组鼻分泌物中 Annexin1 含量均较治疗前显著明显升高($P < 0.05$);与对照组比较,实验组治疗后

鼻分泌物中 Annexin1 含量明显升高,差异有统计学意义($P < 0.05$);与健康组相比,实验组治疗后 Annexin1 含量差异无统计学意义($P > 0.05$)。见表 3。

2.4 各组患者鼻分泌物中 VCAM-1 含量比较

治疗后,实验组和对照组鼻分泌物中 VCAM-1 含量均较治疗前显著下降($P < 0.05$),与对照组比较,实验组治疗后鼻分泌物中 VCAM-1 含量明显降低,差异有统计学意义($P < 0.05$);与健康组相比,实验组治疗后 VCAM-1 含量差异无统计学意义($P > 0.05$),见表 4。

表 2 各组患者治疗前后鼻分泌物中 TNF- α 含量比较($\bar{x} \pm s$)Table 2 Comparison of the TNF- α level in nasal secretions between different group($\bar{x} \pm s$)

Groups	n	Time	TNF- α ($\mu\text{g/mL}$)
Experimental group	46	Before treatment	6.35 $\pm$ 0.86
		After treatment	2.54 $\pm$ 0.33* [#]
Control group	46	Before treatment	6.70 $\pm$ 0.96
		After treatment	4.86 $\pm$ 0.68* [#]
Healthy group	46	-	2.49 $\pm$ 0.35

Note: Compared with before treatment, *P<0.05. Compared with the control group, [#]P<0.05. Compared with the healthy group, ^ΔP<0.05.

表 3 各组患者治疗前后鼻分泌物中 Annexin1 含量比较($\bar{x} \pm s$)Table 3 Comparison of the Annexin1 level in nasal secretions between different group($\bar{x} \pm s$)

Groups	n	Time	Annexin1($\mu\text{g/mL}$)
Experimental group	46	Before treatment	0.47 $\pm$ 0.06
		After treatment	0.73 $\pm$ 0.11* [#]
Control group	46	Before treatment	0.49 $\pm$ 0.04
		After treatment	0.59 $\pm$ 0.05* [#]
Healthy group	46	-	0.75 $\pm$ 0.18

Note: Compared with before treatment, *P<0.05. Compared with the control group, [#]P<0.05. Compared with the healthy group, ^ΔP<0.05.

表 4 各组患者治疗前后鼻分泌物中 VCAM-1 含量比较($\bar{x} \pm s$)Table 4 Comparison of the VCAM-1 level in nasal secretions between different group($\bar{x} \pm s$)

Groups	n	Time	VCAM-1(ng/mL)
Experimental group	46	Before treatment	97.98 $\pm$ 11.07
		After treatment	26.93 $\pm$ 3.75* [#]
Control group	46	Before treatment	97.75 $\pm$ 11.06
		After treatment	56.58 $\pm$ 8.86* [#]
Healthy group	46	-	25.85 $\pm$ 3.63

Note: Compared with before treatment, *P<0.05. Compared with the control group, [#]P<0.05. Compared with the healthy group, ^ΔP<0.05.

2.5 实验组与对照组患者临床疗效比较

对照组患者治疗后临床有效率为 73.91 %(34/46), 实验组

组患者治疗后临床有效率为 91.30 %(42/46), 实验组有效率高于对照组,具有统计学意义(P<0.05)。

表 5 两组患者治疗后临床治疗效果分析(例,%)

Table 5 Comparison of the clinical curative effect between two groups after treatment(n,%)

Groups	Case	Excellence	Effective	Invalid	Clinical curative effect rate
Control group	46	15(32.61 %)	19(41.30%)	12(26.09 %)	34(73.91 %)
Experimental group	46	26(56.52 %)	16(34.78%)	4(8.70 %)	42(91.30 %)
χ^2					4.842
P					0.028

3 讨论

变应性疾病是世界卫生组织确定的 21 世纪需要重点研究和防治的疾病之一, 变应性鼻炎为变应性疾病的重要组成部分,随着环境的污染,变应性鼻炎的发病率呈逐年上升趋势,严重影响患者的身体健康和生活质量。祖国医学在变应性鼻炎的发病机制、辩证治疗以及防护都有着独到的见解,随着疾病的需要,各类治疗变应性鼻炎中药制剂应运而生,且均取得较好的临床疗效^[6-8]。芩蒿滴鼻液是由黄芩、新疆一支蒿及甘草组成的复方制剂,现代药理研究表明^[9-11]黄芩和新疆一支蒿中的黄

酮类化合物如黄芩苷、黄芩素、汉黄芩素、汉黄芩苷及酮酸类、氨基酸类、苷类、倍半萜类及多糖类等化学成分具有明显抗过敏、抗炎和调节机体免疫功能的作用,既能缓解变应性鼻炎患者的临床症状,又能从疾病的本质中调节,防止过敏原的刺激而再犯。

炎症介质 SP 是一种分布于细神经纤维能够诱导神经源性炎症的神经肽,具有复杂的生物活性,主要分布在呼吸道和鼻黏膜上皮之间、固有层血管及腺体周围,能够扩张血管并使血管的通透性增加,导致血浆外渗^[12]。P 物质与靶细胞结合,释放调节肥大细胞受体的介质,最终释放组胺参与变态性反应而

发生变应性鼻炎^[13]。本研究结果显示:AR 患者鼻分泌物中 P 物质的含量较健康组含量明显增高,而通过治疗后,实验组鼻分泌物中 SP 含量明显低于对照组,说明 SP 能够诱导释放组胺并引发过敏反应,而芩蒿滴鼻液能够降低 SP 表达,下调肥大细胞、嗜酸性粒细胞的活化程度,从而降低组胺释放,阻止过敏反应的发生。

肿瘤坏死因子 α (TNF- α)是由单核 - 巨噬细胞系统和内皮细胞产生的细胞因子,参与机体的免疫应答,变应性鼻炎患者含有大量的巨噬细胞、肥大细胞和单核细胞,而这些细胞均有产生 TNF- α 的能力,TNF- α 能够增加血管的通透性,导致鼻黏膜发生充血水肿,并能导致鼻黏膜上皮局部炎症的发生,最终发生过敏性鼻炎^[14]。本研究结果显示,AR 患者鼻分泌物中 TNF- α 的含量明显高于健康组,且治疗后,实验组 TNF- α 含量明显低于对照组,说明芩蒿滴鼻液能够显著降低 AR 患者 TNF- α 的表达。芩蒿滴鼻液能够抑制巨噬细胞、单核细胞和肥大细胞的生长、发育,防止炎症细胞黏附于血管壁,减轻患者鼻黏膜水肿,缓解 AR 患者症状^[15]。

膜联蛋白 1(Annexin1)是一种能够抑制炎症发生转化的炎症调控蛋白,在炎症物质的产生过程中有着重要的作用,Annexin1 能够移动黏附于血管壁的单核细胞和中性粒细胞,减轻炎症反应,从而缓解 AR 患者临床症状^[16,17]。本研究结果显示:变应性鼻炎患者鼻分泌物中 Annexin1 的含量明显低于健康组,而经过治疗后,实验组患者鼻分泌物中 Annexin1 含量明显高于对照组,并与健康组相当。说明芩蒿滴鼻液能够上调 Annexin1 水平,这可能与芩蒿滴鼻液能够抑制单核细胞和中性粒细胞黏附于血管壁,阻止炎症因子的形成,从而促进 Annexin1 的产生^[18]。

血细胞粘附因子 -1(VCAM-1)是一种具有促进嗜酸性粒细胞黏附于血管壁的黏附因子,VCAM-1 能够与嗜酸性粒细胞表面受体结合,促进嗜酸性粒细胞的迁移,参与变态反应^[19]。本研究结果显示:AR 患者鼻分泌物中 VCAM-1 的含量明显高于健康组,且治疗后,实验组 VCAM-1 含量明显低于对照组,说明 VCAM-1 参与变应性鼻炎的产生,而芩蒿滴鼻液能够显著降低 VCAM-1 的表达。芩蒿滴鼻液能够抑制嗜酸性粒细胞在血管壁的黏附、活化,减少炎症细胞聚集到粘膜炎症部位,缓解鼻黏膜充血水肿,提高临床治疗效果^[20]。

综上所述,芩蒿滴鼻液能够抑制变应性鼻炎患者巨噬细胞、嗜酸性粒细胞、单核细胞的活化、迁移,阻止炎症细胞黏附于血管壁,降低组胺释放,阻止过敏反应的发生,从而下调炎症介质 SP、TNF- α 、VCAM-1 在鼻黏膜的表达,上调 Annexin1 的表达,缓解患者鼻黏膜充血水肿,提高临床治疗疗效。

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又使内皮细胞之活化形式发生改变,促进肿瘤细胞更容易穿过基质,进而诱发肿瘤浸润及转移的发生。

综上所述,RegIV 在视网膜母细胞瘤中呈高表达,且与肿瘤的侵袭与转移相关,其可能通过促进 VEGF-A、VEGF-C 表达促进血管新生,进而加速视网膜母细胞瘤的发生和进展。因此,我们可以通过减少 RegIV、VEGF-A、VEGF-C 的表达,抑制血管新生,进而阻止视网膜母细胞瘤的浸润与转移。

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(上接第 76 页)

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