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酮替芬联合沙丁胺醇气雾剂喷吸对咳嗽变异性哮喘患者嗜酸性粒细胞趋化因子与肺功能的影响*

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摘要 目的：探讨酮替芬联合沙丁胺醇气雾剂喷吸对咳嗽变异性哮喘患者嗜酸性粒细胞趋化因子与肺功能的影响。**方法：**选择2015年3月到2016年4月我院接诊的98例咳嗽变异性哮喘患者研究，按抽签法将其随机分为观察组和对照组，每组49例。对照组患者给予沙丁胺醇气雾剂、氨茶碱治疗，观察组在对照组基础上给予酮替芬治疗。观察比较治疗前后两组临床疗效；白天及夜间咳嗽症状评分；嗜酸性粒细胞（EOS）计数和嗜酸性粒细胞趋化因子（Eotaxin）水平；肺功能相关评价指标（FVC、FEV1、PEF）。**结果：**治疗后，观察组有效率（93.88%）高于对照组（79.59%），差异有统计学意义（*P<0.05*）。两组白天及夜间咳嗽症状评分均显著下降，观察组下降更为明显[（0.77± 0.39）VS（0.99± 0.52）、（0.87± 0.32）VS（1.07± 0.34）]，差异有统计学意义（*P<0.05*）；两组EOS计数和Eotaxin水平均明显下降，观察组下降更为显著[（188.47± 30.39）VS（232.59± 30.52）、（169.44± 27.79）VS（191.07± 34.34）]，差异具有统计学意义（*P<0.05*）；两组相关评价指标（FVC、FEV1、PEF）均明显提高，观察组相关指标值提高更为显著[（3.99± 0.39）VS（3.87± 0.12）、（3.87± 0.79）VS（3.52± 0.39）、（7.99± 1.98）VS（7.34± 1.01）]，差异有统计学意义（*P<0.05*）。**结论：**酮替芬联合沙丁胺醇气雾剂喷吸对咳嗽变异性哮喘的疗效显著，能明显降低患者嗜酸性粒细胞趋化因子的水平，显著改善患者的肺功能，值得临床推广运用。

关键词：咳嗽变异性哮喘；酮替芬；沙丁胺醇；嗜酸性粒细胞趋化因子；肺功能

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Effect of Ketotifen Combined with Salbutamol Aerosol Spraying on Eotaxin and Pulmonary Function in Cough Variant Asthma Patients*

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ABSTRACT Objective: To investigate the effect of ketotifen and salbutamol aerosol on eosinophil and lung function in patients with cough variant asthma. **Methods:** A total of 98 cough variant asthma patients admitted to our hospital from March 2015 to April 2016 were randomly divided into observation group and control group according to random sampling method, with 49 cases in each group. Patients in the control group were given albuterol aerosol and aminophylline, and the observation group was given ketotifen on the basis of the control group. The clinical curative effect was observed and compared between the two groups before and after treatment. The scores of cough symptom at daytime and nighttime, the eosinophil count (EOS) and Eotaxin level, and the pulmonary function related evaluation index (FVC, FEV1, PEF) were observed. **Results:** After treatment, the effective rate of the observation group (93.88%) was higher than that of the control group (79.59%), the difference was statistically significant (*P <0.05*). The cough symptom scores of both groups were significantly decreased during the day and night, and the decrease in the observation group was more significant [(0.77 ± 0.39) vs (0.99 ± 0.52), (0.87 ± 0.32) vs(1.07 ± 0.34)], respectively(*P <0.05*). The EOS counts and Eotaxin levels in both groups were significantly decreased, and the decrease in the observation group was more significant [(188.47 ± 30.39)vs(232.59 ± 30.52), (169.44 ± 27.79) vs(191.07 ± 34.34)] , respectively (*P <0.05*). The relative indexes (FVC, FEV1, PEF) in both groups were significantly higher than those in the control group [(3.99 ± 0.39)vs(3.87 ± 0.12), (3.87 ± 0.79) vs 3.52 ± 0.39, (7.99 ± 1.98) VS (7.34 ± 1.01)], the difference was statistically significant (*P <0.05*). **Conclusion:** Ketotifen combined with salbutamol aerosol spray has no significant effect on cough variant asthma Significant effect, can significantly reduce the level of eotaxin in patients with significant improvement in patients with lung function, it is worth promoting clinical application.

Key words: Cough variant asthma; Ketotifen; Salbutamol; Eotaxin; Pulmonary function

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咳嗽变异性哮喘(Cough variant asthma，CVA) 属于支气管哮喘的一种特殊类型，又称为咳嗽型哮喘，临床上以持续性咳嗽为其主要或者唯一的症状[1,2]。CVA 患者容易受到气候变化、冷空气、运动的影响或者由呼吸道感染而出现发作性的咳嗽或原有咳嗽加重，由于其发作时缺乏典型的哮喘症状而容易漏诊或误诊为上呼吸道感染、支气管炎，导致患者错过了最佳治疗时机，部分患者可能发展为典型的哮喘[3,4]。对于咳嗽变异性哮喘的治疗，目前临床上还没有统一的治疗方案，此前使用抗生素及止咳药物对患者进行治疗时无明显疗效。对于 CVA 的发病机制也尚无统一的研究结论，但大量国内外研究显示 CVA 与患者气道持续性的炎症反应及高反应性具有明显的相关性，其中嗜酸性粒细胞分泌的嗜酸性粒细胞趋化因子在咳嗽变异性哮喘的发生、发展中发挥着重要作用[5,6]。据相关临床药理研究显示，沙丁胺醇气雾剂属于 β2 受体激动剂，具有支气管扩张作用，能明显的缓解支气管的痉挛；酮替酚属于组胺受体(H1)拮抗剂，能够减轻气道的炎症反应并降低其高反应性，改善患者的相应症状，从而改善肺功能，与 β2 受体激动剂联用时具有协同作用[7,8]。而检索国内关于酮替芬联合沙丁胺醇气雾剂喷吸对咳嗽变异性哮喘患者嗜酸性粒细胞趋化因子与肺功能的影响的相关报道较少，不利于临床的指导治疗，本研究将酮替芬与沙丁胺醇气雾剂联合用于咳嗽变异性哮喘患者的治疗研究中，以探讨其对患者的嗜酸性粒细胞趋化因子与肺功能的影响。

1 材料与方法

1.1 一般材料

入选的研究对象选择 2015 年 3 月到 2016 年 4 月我院接诊的 98 例咳嗽变异性哮喘患者研究，按抽签法将其随机分为观察组和对照组，每组 49 例。其中实验组男性患者 27 例、女性患者 22 例，年龄在 19 岁 ~47 岁之间，平均年龄为(32.1± 3.8)岁，平均病程为(9.6± 1.1)年；对照组男性患者 24 例、女性患者 25 例，年龄在 18 岁 ~46 岁之间，平均年龄为(31.9± 3.6)岁，平均病程为(9.8± 1.0)年。两组基本资料比较，差异均无统计学意义($P>0.05$)，具有可比性。

纳入标准[9]：所有患者均符合中华医学会呼吸病学分会哮喘学组 2016 年制定的《支气管哮喘防治指南》。以咳嗽作为唯一或主要症状，无喘息、气急等典型哮喘的症状和体征，同时具备可变气流受限客观检查中的任一条，除外其他疾病。

排除标准[10]：① 合并有严重的心、肝、肾、脑疾病病史的患者；② 合并有呼吸系统其他引起慢性咳嗽的疾病；③ 近 3 个月内有严重感染性疾病，使用过糖皮质激素者；④ 对酮替芬与沙丁胺醇气雾剂过敏者；⑤ 孕妇及妊娠妇女或有精神疾病者。

1.2 方法

将入选患者随机分为实验组和对照组，对照组患者给予沙丁胺醇气雾剂(葛兰素史克制药(重庆)有限公司，批准文号：国药准字 H10940001，用法：每次喷吸 100~200 μg(即 1~2 喷)，咳嗽症状较严重时可隔 4 小时重复喷吸 1 次，但 1 天内不超过 4 次。观察组在对照组基础上给予酮替芬(富马酸酮替芬片，海南制药厂有限公司制药一厂，批准文号：国药准字 H41023929，10 mg/ 片，用法：口服，1 片 / 次，1 次 /d。)进行治疗。两组患者均持续治疗 40 天。

1.3 观察指标

1.3.1 疗效观察 显效：患者的临床症状得到明显改善甚至消失，未出现复发现象；有效：患者的临床症状有所改善，基本无复发现象；无效：患者的临床症状未得到改善甚至有所加重倾向。其中治疗的总有效率 =(显效 + 有效)/ 总病例数× 100%。

1.3.2 指标测定 (1)CVA 患者咳嗽症状评分(白天及夜间积分标准一致)：无咳嗽记为 0 分；偶尔发作性短暂咳嗽记为 1 分；频繁持续性咳嗽、对患者生活造成轻微影响记为 2 分；频繁持续性咳嗽、对患者日常生活造成严重影响记为 3 分。

(2) 于清晨提取两组患者的 5 mL 静脉血置于抗凝试管中待检。嗜酸粒细胞(Eos)计数：取 2 mL 静脉血通过血液细胞分析仪(深圳市盛信康科技有限公司，型号 Sysmex XE-2100)计数外周血中的嗜酸性粒细胞(Eos)。血清嗜酸粒细胞趋化因子(Eotaxin) 测定：将抗凝试管中剩余 3 mL 静脉血静置半小时后，与 2000 r/min 的条件下离心 20 min，静置后取上层血清于 -80℃条件下冷冻保存，使用 Eotaxin 试剂盒(上海江莱生物科技有限公司，试剂盒灵敏度：5 ng/L)通过 ELISA 法检测两组患者血清中的嗜酸粒细胞趋化因子(Eotaxin)水平，检测过程按照 Eotaxin 试剂盒使用说明严格进行操作。肺功能测定：通过肺功能仪(英国迈科医疗公司，国械注进 20142405821，型号：Micro Lab)对两组患者的肺功能相关指标[用力肺活量(Fatigue capacity，FVC)、第一秒用力呼气容积(The first second forced expiratory volume，FEV1)、呼气峰流速 (Expiratory peak flow rate，PEF)]进行检测。

1.4 统计学分析

本研究的数据选用 SPPS18.0 进行处理，计量资料以均数± 标准差($\bar{x}\pm s$)表示，组间选用独立样本 t 检验进行比较，计数资料用[(例)%]表示计数资料，组间选用 x^2 检验进行比较，$P<0.05$ 为有统计学意义。

2 结果

2.1 两组临床疗效比较

对照组及观察组的临床疗效有效率分别为 79.59%、93.88%，实验组有效率明显高于对照组，组间差异显著 ($P<0.05$)，见表 1。

2.2 两组治疗前后咳嗽症状评分比较

治疗前，两组白天及夜间咳嗽症状评分比较均无差异($P>0.05$)；治疗后，两组白天及夜间咳嗽症状评分均显著下降，观察组下降更为明显($P<0.05$)，见表 2。

2.3 两组治疗前后 EOS 计数和 Eotaxin 水平比较

治疗前，两组 EOS 计数和 Eotaxin 水平比较均无差异($P>0.05$)；治疗后，两组 EOS 计数和 Eotaxin 水平均明显下降，观察组下降更为显著($P<0.05$)，见表 3。

2.4 两组治疗前后肺功能相关评价指标比较

治疗前，两组肺功能相关评价指标(FVC、FEV1、PEF)比较均无差异($P>0.05$)；治疗后，两组相关评价指标(FVC、FEV1、PEF)均明显提高，观察组相关指标值提高更为显著($P<0.05$)，见表 4。

表 1 两组临床疗效比较[(例)%]

Table 1 Comparison of the clinical effects of two groups [(n)%]

Groups	n	Effective	Valid	Invalid	Total effective rate
Observation group	49	39(79.59)	7(14.29)	3(6.12)	46(93.88)
Control group	49	19(38.78)	20(40.82)	10(20.41)	39(79.59)
u/x^2			u=4.0093		x^2=4.3457
P			P=0.0001		P=0.0371

表 2 两组治疗前后咳嗽症状评分比较($\bar{x}\pm s$)

Table 2 Comparison of the cough symptom score of two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	Cough symptom score	
			Day	Night
Observation group	49	Before treatment	2.70± 0.41	2.93± 0.28
		After treatment	0.77± 0.39	0.87± 0.32
Control group	49	Before treatment	2.77± 0.32	2.88± 0.39
		After treatment	0.99± 0.52	1.07± 0.34
t/p inter group value		Before treatment	0.9421,0.3485	0.7290,0.4678
		After treatment	2.3692,0.0198	2.9985,0.0035

表 3 两组治疗前后 EOS 计数和 Eotaxin 水平比较($\bar{x}\pm s$)

Table 3 Comparison of the EOS and Eotaxin of two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	EOS(10^6/L)	Eotaxin(ng/L)
Observation group	49	Before treatment	591.52± 98.41	215.53± 73.28
		After treatment	188.47± 30.39	169.44± 27.79
Control group	49	Before treatment	591.47± 98.32	215.38± 73.39
		After treatment	232.59± 30.52	191.07± 34.34
t/p inter group value		Before treatment	0.0025,0.9980	0.0101,0.9919
		After treatment	7.1707,0.0000	3.4274,0.0009

表 4 两组治疗前后肺功能相关评价指标比较($\bar{x}\pm s$)

Table 4 Comparison of thepulmonary function evaluation index of two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	FVC(L)	FEV1(L)	PEF(L)
Observation group	49	Before treatment	3.52± 0.71	3.13± 0.28	6.07± 2.03
		After treatment	3.99± 0.39	3.87± 0.79	7.99± 1.98
Control group	49	Before treatment	3.57± 0.67	3.11± 0.34	6.11± 2.00
		After treatment	3.87± 0.12	3.52± 0.39	7.34± 1.01
t/p inter group value		Before treatment	0.3585,0.7207	0.3179,0.7513	0.0983,0.9219
		After treatment	2.0586,0.0422	2.7809,0.0065	2.0470,0.0434

3 讨论

咳嗽变异性哮喘（CVA）属于支气管哮喘的一种特殊类型，又称为咳嗽型哮喘，临床上以持续性咳嗽为其主要或者唯一的症状，CVA 患者容易受到气候变化、冷空气、运动的影响或者由呼吸道感染而出现发作性的咳嗽或原有咳嗽加重，由于其发作时缺乏典型的哮喘症状而容易漏诊或误诊为上呼吸道感染、支气管炎，导致患者错过了最佳治疗时机，部分患者可能发展为典型的哮喘[11,12]。因此研究清楚该病的发病机制并给与安全有效合理的治疗措施是改善患者健康状况、防止病情进一步发展的关键所在。

国内外相关研究发现，咳嗽变异性哮喘与典型性哮喘具有基本一致的发病机制。其中就包括了气道炎症反应即气道上皮浸润着大量以嗜酸性粒细胞为主的炎性细胞和气道的高反应性以及进一步发展导致的气道重塑等[13,14]。在咳嗽变异性哮喘的发生、发展中，许多细胞因子在其中发挥着重要作用，嗜酸粒

细胞趋化因子(Eotaxin)便是其中的一种关键性细胞因子,在正常的呼吸道内,嗜酸粒细胞趋化因子主要是由气道上皮细胞产生,但当机体处于病理状态下,气道发生病理性改变时,嗜酸粒细胞受到抗原刺激后,替代气道上皮细胞而成为嗜酸粒细胞趋化因子的主要来源[15,16]。大量研究显示,Eotaxin 在咳嗽变异性哮喘的发生发展中起到的关键性作用主要是通过趋化嗜酸性粒细胞并导致其在肺内的大量募集,促进嗜酸性粒细胞在微血管内皮细胞上的黏附作用,最终活化而脱颗粒产生颗粒蛋白,从而对肺组织造成严重的损伤[17,18]。据相关的研究显示,Eotaxin 在支气管哮喘的患者体内,其表达作用明显的增强,与嗜酸性粒细胞的计数具有一定的正相关性[19,20]。因此在对 CVA 患者的治疗中,计数 Eos 及检测 Eotaxin 在患者体内的水平也能在一定程度上反应相应治疗措施及药物的疗效,也为以后的 CVA 患者的临床治疗提供一定的指导。另外对患者的肺功能的检查是一种简便、安全并能直观反应患者病情的一项措施,研究显示咳嗽变异性哮喘的肺功能损害程度介于典型性哮喘与正常肺功能状态之间,肺通气功能的改变能反应治疗过程中相应药物的疗效。其中肺功能检查主要包括 FVC、FEV1、PEF 等,其中 PEF 是反应患者小气道高反应性的病理生理改变的一项重要参数,具有一定的特异性[21,22]。

此前的相关临床试验显示,传统的治疗中使用抗生素及止咳药物对患者进行治疗疗效不明显[23,24],而临床上对于 CVA 患者的治疗措施尚无统一的标准。近年来,随着医学的发展,大量的临床实践及研究显示,沙丁胺醇气雾剂在 CVA 患者的治疗能取得相对较好的疗效[25,26]。据相关药理研究表明,沙丁胺醇气雾剂属于一种选择性的 β2 受体激动剂,通过选择性的激动气道平滑肌细胞膜上的 β2 受体,抑制炎症介质的释放,对支气管产生较强的扩张作用[27,28]。酮替芬属于一种细胞膜稳定剂,同时也是组胺受体 H1 拮抗剂,具有很强的抗组胺作用,能抑制变态反应相关介质的释放,还能预防和逆转 β2 受体的向下调节,与 β2 受体激动剂联用后具有协调作用,可促进支气管的扩张、加强机体 β2 受体的敏感性[29,30]。本研究将酮替芬与沙丁胺醇气雾剂联合用于 CVA 患者的治疗中,研究结果显示将酮替芬联合沙丁胺醇气雾剂喷吸治疗的观察组患者的临床疗效显著高于对照组,治疗后其白天及夜间的咳嗽症状评分降低也较对照下降明显,Eos 计数及 Eotaxin 水平也较对照组下降明显,肺功能改善也较对照组明显。由此可见将酮替芬与沙丁胺醇气雾剂合用与咳嗽变异性哮喘患者的治疗中既有较好的抗炎作用,能明显的扩张支气管、缓解其痉挛状态的作用,同时还具有相对较强的抗过敏作用,明显改善患者的咳嗽症状、降低嗜酸性粒细胞趋化因子水平,明显改善肺功能。

综上所述,酮替芬联合沙丁胺醇气雾剂喷吸对咳嗽变异性哮喘的疗效显著,能明显降低患者嗜酸性粒细胞趋化因子的水平,显著改善患者的肺功能,值得临床推广运用。

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