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多索茶碱联合盐酸氨溴索治疗老年稳定期 COPD 的临床疗效及对血清 IL-33/sST2 轴表达的影响

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[摘　要]　**目的：**探讨多索茶碱联合盐酸氨溴索治疗老年稳定期慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)的临床疗效及对血清IL-33/sST2轴表达的影响。**方法：**选择2020年1月至2022年1月无锡市锡山人民医院门诊收治的110例老年稳定期COPD患者，随机分为对照组与试验组，每组55例。对照组给予单纯多索茶碱治疗，试验组给予多索茶碱联合盐酸氨溴索治疗。比较两组的临床疗效、治疗前后肺功能、外周血IL-33、sST2的mRNA和蛋白表达水平、血清炎症因子水平及不良反应发生率。**结果：**试验组治疗总有效率为94.55%(52/55)，高于对照组的74.55%(41/55；P<0.05)。试验组治疗14 d后第1秒用力呼气容积(forced expiratory volume in 1 second，FEV_1)、用力肺活量(forced vital capacity，FVC)、FEV_1/FVC及呼气峰值流速(peak expiratory flow，PEF)水平分别为(1.97±0.28) L、(3.50±0.37) L、0.74±0.10、(3.53±0.52) L/s，均高于对照组(均P<0.05)。试验组治疗14 d后IL-33、sST2的mRNA表达水平分别为1.20±0.24、1.10±0.19，IL-33、sST2的蛋白水平分别为(382.07±35.40) pg/mL、(567.37±54.51) pg/mL，均低于对照组(均P<0.05)。试验组治疗14 d后外周血IL-6、IL-8、CRP、TNF-α水平分别为(5.94±0.98) ng/L、(251.06±12.28) ng/L、(4.71±0.92) mg/L、(11.98±2.12) pg/L，均低于对照组(均P<0.05)。试验组治疗总不良反应发生率为7.27%(4/55)，低于对照组的21.82%(12/55；P<0.05)。**结论：**多索茶碱联合盐酸氨溴索治疗老年稳定期COPD患者疗效确切，可改善肺功能，抑制血清IL-33/sST2轴表达水平，降低炎症因子水平，且不良反应小，安全可靠。

[关键词]　多索茶碱；盐酸氨溴索；老年；慢性阻塞性肺疾病；疗效；IL-33/sST2轴表达；肺功能；不良反应

Clinical efficacy of doxofylline combined with ambroxol hydrochloride in the treatment of elderly patients with stable COPD and its effect on the expression of serum IL-33/sST2 axis

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Abstract　**Objective:** To investigate the clinical efficacy of doxofylline combined with ambroxol hydrochloride in the

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treatment of elderly patients with stable chronic obstructive pulmonary disease (COPD) and its effect on the expression of serum IL-33/sST2 axis. **Methods:** A total of 110 elderly patients with stable COPD who were admitted to the outpatient clinic of Xishan People's Hospital of Wuxi from January 2020 to January 2022 were selected and randomly divided into the control group and the experimental group, with 55 cases in each group. The control group was given doxofylline alone, and the experimental group was given doxofylline combined with ambroxol hydrochloride. The clinical efficacy, lung function, IL-33, sST2 mRNA and protein expression levels, serum inflammatory factor levels and incidence of adverse reactions were compared between the 2 groups before and after the treatment. **Results:** The total effective rate in the experimental group was 94.55% (52/55), which was higher than 74.55% (41/55) in the control group (P<0.05). After 14 days of treatment, the levels of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and peak expiratory flow (PEF) in the experimental group were (1.97±0.28) L, (3.50±0.37) L, 0.74±0.10, (3.53±0.52) L/s, which were higher than those in the control group (all P<0.05). After 14 days of treatment in the experimental group, the mRNA expression levels of IL-33 and sST2 were (1.20±0.24) and (1.10±0.19), respectively, and the protein levels of IL-33 and sST2 were (382.07±35.40) pg/mL, (567.37±0.19) pg/mL, all lower than the control group (all P<0.05). The levels of IL-6, IL-8, CRP and TNF-α in the experimental group after 14 days of treatment were (5.94±0.98) ng/L, (251.06±12.28) ng/L, (4.71±0.92) mg/L, (11.98±2.12) pg/L, all lower than the control group (all P<0.05). The total adverse reaction rate in the experimental group was 7.27% (4/55), which was lower than 21.82% (12/55) in the control group (P<0.05). **Conclusion:** Doxofylline combined with ambroxol hydrochloride is effective in the treatment of elderly patients with stable COPD, can improve lung function, inhibit the expression level of serum IL-33/sST2 axis, reduce the level of inflammatory factors, and has few adverse reactions, which is safe and reliable.

Keywords doxofylline; ambroxol hydrochloride; elderly; chronic obstructive pulmonary disease; efficacy; IL-33/sST2 axis expression; pulmonary function; adverse reactions

慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)属高发疾病，具有高病死率。稳定期COPD患者虽然病情能够得到控制，但仍需给予有效药物进行治疗[1]。去痰止咳、解痉平喘及抗感染等措施，但长期疗效不佳，且会对患者免疫功能造成影响[2-3]。2015年慢性阻塞性肺病全球倡议(Global Initiative for Chronic Obstructive Lung Disease，GOLD)颁布的“慢性阻塞性肺疾病指南”推荐使用长效β受体激动剂治疗，但长效β受体激动剂会刺激交感神经，长期服用有患心血管疾病风险，长效胆碱能拮抗剂虽然可以抑制副交感神经，但会造成局部缺血、心律失常。因此寻找有效且安全的治疗药物具有重要意义。茶碱类药物是目前临床常用COPD患者治疗药物，有抗支气管痉挛、抗感染等作用；盐酸氨溴索作为一种黏液溶解剂，能够帮助患者排痰，改善通气功能[4-5]。本研究对无锡市锡山人民医院选取的老年稳定期COPD患者给予多索茶碱联合盐酸氨溴索治疗，并与单纯应用多索茶碱进行比较，现报道如下。

1 对象与方法

1.1 对象

选择2020年1月至2022年1月无锡市锡山人民医院门诊收治的110例老年稳定期COPD患者。纳入标准：1)年龄>60周岁；2)经影像学检查、实验室检查结合临床症状确诊为COPD；3)疾病处于稳定期；4)患者及家属均签署知情同意书。排除标准：1)合并严重心、脑、肾、肝等脏器功能障碍；2)合并严重代谢性疾病；3)对使用药物过敏；4)合并严重感染；4)既往精神疾病史；5)治疗依从性差；6)合并血液系统疾病；7)近4周接受其他药物治疗。将患者随机分为对照组与试验组，每组55例。本研究经无锡市锡山人民医院医学伦理委员会批准通过(审批号：xs2019ky008)。

1.2 方法

对照组给予多索茶碱(浙江北生药业汉生制药有限公司，国药准字H20040617) 0.3 g+100 mL生理盐水，静脉滴注，2次/d，持续2周。试验组在

对照组治疗的基础上给予盐酸氨溴索(山东鲁抗医药集团赛特有限责任公司/山东致泰医药技术有限公司，国药准字H20223104) 30 mg+5%葡萄糖注射液250 mL，静脉滴注，1次/d，持续2周。

1.3 观察指标

1)疗效判定标准。显效：患者治疗后咳嗽、气短、胸闷等临床症状基本消失，第1秒用力呼气容积(forced expiratory volume in 1 second，FEV_1)较治疗前增加25%~35%。有效：患者治疗后上述症状有所缓解，FEV_1较治疗前增加15%~25%。无效：患者治疗后上述症状无任何改善，甚至加重[6]。总有效=显效+有效。2)肺功能。采用德国耶格普及型肺功能仪Master Scope检测并记录两组治疗前、治疗14 d后FEV_1、用力肺活量(forced vital capacity，FVC)、FEV_1/FVC及呼气峰值流速(peak expiratory flow，PEF)水平。3)外周血IL-33、sST2的mRNA相对表达水平。采集患者清晨空腹肘静脉血，采用荧光定量PCR法检测并记录两组治疗前、治疗14 d后IL-33、sST2的mRNA水平；采用酶联免疫吸附法检测并记录两组治疗前、治疗14 d后外周血IL-33、sST2的蛋白水平。4)血清炎症因子水平。采用酶联免疫吸附法检测并记录两组治疗前、治疗14 d后外周血IL-6、IL-8、CRP及TNF-α水平。5)不良反应。记录两组治疗期间恶心呕吐、消化不良、头痛、皮疹等不良反应发生率情况。

1.4 统计学处理

采用SPSS 22.0统计软件进行分析。计量资料均符合正态分布及方差齐性，采用均数±标准差($\bar{x}\pm s$)表示，组间比较应用t检验。计数资料采用例(%)表示，χ^2检验或Fisher精确概率法。P<0.05为差异有统计学意义。

2 结果

2.1 两组一般资料比较

两组一般资料比较差异均无统计学意义(均P>0.05，表1)。

2.2 两组疗效比较

试验组治疗总有效率为94.55%，高于对照组的74.55%(P<0.05，表2)。

2.3 两组肺功能比较

治疗14 d后，两组FEV_1、FVC、FEV_1/FVC及PEF水平均显著提高，且试验组治疗14 d后FEV_1、FVC、FEV_1/FVC及PEF水平均高于对照组(均P<0.05，表3)。

2.4 两组 IL-33、sST2 的 mRNA 相对表达水平比较

治疗14 d后，两组IL-33、sST2的mRNA和蛋白表达水平均显著降低，且试验组治疗14 d后IL-33、sST2的mRNA和蛋白表达水平均低于对照组(均P<0.05，表4)。

2.5 两组血清炎症因子水平比较

治疗14 d，两组后IL-6、IL-8、CRP、TNF-α水平均显著降低，且试验组治疗14 d后IL-6、IL-8、CRP、TNF-α水平均低于对照组(均P<0.05，表5)。

2.6 两组不良反应比较

试验组治疗总不良反应发生率为7.27%，低于对照组的21.82%(P<0.05，表6)。

表1 两组一般资料比较(n=55)

Table 1 Comparison of general data between the 2 groups (n=55)

组别	性别(男/女)/例	年龄/岁	病程/年	平均体重指数/($kg\cdot m^{-2}$)	合并症/例			
					糖尿病	高脂血症	高血压	冠心病
对照组	30/25	69.38 ± 7.72	3.66 ± 0.75	24.47 ± 1.34	17	14	12	8
观察组	32/23	70.22 ± 8.07	3.70 ± 0.77	24.66 ± 1.05	16	15	10	9
χ^2/t	0.148	0.558	0.276	0.828	0.296			
P	0.701	0.578	0.783	0.410	0.961			

表2 两组临床疗效比较(n=55)

Table 2 Comparison of clinical efficacy between the 2 groups (n=55)

组别	显效/[例(%)]	有效/[例(%)]	无效/[例(%)]	总有效/[例(%)]
对照组	20 (36.36)	21 (38.18)	14 (25.45)	41 (74.55)
试验组	29 (52.73)	23 (41.82)	3 (5.45)	52 (94.55)
χ^2	—	—	—	8.419
P	—	—	—	0.004

表3 两组治疗前后肺功能比较(n=55)

Table 3 Comparison of lung function between the 2 groups before and after the treatment (n=55)

时间	组别	FEV_1/L	FVC/L	FEV_1/FVC	PEF/(L·s^{-1})
治疗前	对照组	1.17 ± 0.22	1.84 ± 0.27	0.53 ± 0.08	2.25 ± 0.28
	试验组	1.18 ± 0.24	1.86 ± 0.29	0.52 ± 0.07	2.27 ± 0.31
	t	0.228	0.374	0.698	0.355
	P	0.820	0.709	0.487	0.723
治疗14 d后	对照组	1.59 ± 0.25*	2.21 ± 0.31*	0.61 ± 0.09*	3.02 ± 0.45*
	试验组	1.97 ± 0.28*	3.50 ± 0.37*	0.74 ± 0.10*	3.53 ± 0.52*
	t	7.508	19.820	7.166	5.500
	P	<0.001	<0.001	<0.001	<0.001

与同组治疗前相比，*P<0.05。

Compared with the same group before treatment, *P<0.05.

表4 两组治疗前后IL-33、sST2 mRNA相对表达水平比较(n=55)

Table 4 Comparison of the relative expression levels of IL-33 and sST2 mRNA between the 2 groups before and after the treatment (n=55)

时间	组别	mRNA水平/(pg·mL^{-1})		蛋白水平/(pg·mL^{-1})	
		IL-33	sST2	IL-33	sST2
治疗前	对照组	2.65 ± 0.51	2.19 ± 0.50	479.93 ± 51.28	726.02 ± 74.15
	试验组	2.62 ± 0.49	2.16 ± 0.52	481.05 ± 54.39	722.27 ± 76.03
	t	0.315	0.308	0.111	0.262
	P	0.754	0.758	0.912	0.794
治疗14 d后	对照组	1.64 ± 0.33*	1.38 ± 0.21*	405.69 ± 42.14*	634.81 ± 62.29*
	试验组	1.20 ± 0.24*	1.10 ± 0.19*	382.07 ± 35.40*	567.37 ± 54.51*
	t	7.997	7.333	3.183	6.042
	P	<0.001	<0.001	0.002	<0.001

与同组治疗前相比，*P<0.05。

Compared with the same group before treatment, *P<0.05.

表5 两组治疗前后血清炎症因子水平比较(n=55)

Table 5 Comparison of serum inflammatory factor levels between the 2 groups before and after the treatment (n=55)

时间	组别	IL-6/(ng·L^{-1})	IL-8/(ng·L^{-1})	CRP/(mg·L^{-1})	TNF-α/(pg·L^{-1})
治疗前	对照组	13.04 ± 2.07	419.36 ± 9.57	23.93 ± 4.17	29.06 ± 4.31
	试验组	13.10 ± 2.13	417.59 ± 9.29	24.15 ± 4.52	29.33 ± 4.46
	t	0.150	0.984	0.265	0.323
	P	0.881	0.327	0.791	0.747
治疗14 d后	对照组	8.92 ± 1.27*	305.38 ± 13.27*	9.04 ± 1.36*	17.15 ± 2.07*
	试验组	5.94 ± 0.98*	251.06 ± 12.28*	4.71 ± 0.92*	11.98 ± 2.12*
	t	13.777	22.281	19.557	12.940
	P	<0.001	<0.001	<0.001	<0.001

与同组治疗前相比，*P<0.05。

Compared with the same group before treatment, *P<0.05.

表6 两组不良反应发生率比较(n=55)

Table 6 Comparison of the incidence of adverse reactions between the 2 groups (n=55)

组别	恶心呕吐/[例(%)]	消化不良/[例(%)]	头痛/[例(%)]	皮疹/[例(%)]	总发生/[例(%)]
对照组	4 (7.27)	3 (5.45)	3 (5.45)	2 (3.64)	12 (21.82)
试验组	2 (3.64)	1 (1.82)	1 (1.82)	0 (0.00)	4 (7.27)
χ^2	—	—	—	—	4.681
P	—	—	—	—	0.031

3 讨论

近年来随着全球环境污染状况的日益加重及我国人口老龄化进程的加快，COPD发病率显著上升[7]。COPD患者常见症状为咳痰、咳嗽、气喘等，急性发作期需给予及时有效处理以避免对患者机体造成严重危害，而在稳定期需给予持续药物治疗以避免患者肺功能进一步受损[8-9]。多索茶碱是甲基黄嘌呤衍生物，作为支气管抑制剂，能够有效松弛患者支气管平滑肌，缓解支气管平滑肌痉挛收缩症状[10-11]。盐酸氨溴索能够很好地润滑患者呼吸道，有溶解黏痰的作用[12]。本研究通过对老年稳定期COPD患者实施多索茶碱联合盐酸氨溴索治疗取得了显著效果。

相较于对照组，试验组治疗总有效率更高，且试验组治疗14 d后FEV_1、FVC、FEV_1/FVC及PEF水平均较对照组有明显提高。这表明采用多索茶碱联合盐酸氨溴索治疗可取得更好临床疗效，患者肺功能改善更为明显。原因主要为：盐酸氨溴索作为临床使用率较高的祛痰剂，能够有效改善患者呼吸通道，促进气道引流，利于患者生成肺部表面活性物质，从而提升肺部绒毛摆动频率[13]。此外，盐酸氨溴索能够调节患者黏液及浆液的分泌量，从而起到迅速运输黏液，稀释痰液的作用[14]。有研究[15]显示：盐酸氨溴索可促进黏液保持充分流动性，恢复支气管上皮细胞活性，从而改善气道分泌的物理状态及支气管黏膜分泌活动。而多索茶碱作为一种支气管抑制剂，能够作用于患者支气管，对平滑肌细胞磷酸二酯酶起到显著抑制作用，从而阻断腺苷受体，阻碍平滑肌细胞内钙离子移动，进而有效舒张患者支气管平滑肌，同时还具有镇咳效果[16]。盐酸氨溴索与多索茶碱联合治疗能够促进气道内稀释痰液，使气道阻力降低，改善呼吸状态，最终改善肺功能。本研究显示：两组治疗14 d后IL-33、sST2的mRNA和蛋白表达水平均显著降低，且试验组降低更明显(P<0.05)。这表明多索茶碱联合盐酸氨溴索治疗能够显著抑

制血清IL-33/sST2轴表达水平。其主要原因为：IL-33通常表达于人体胃肠道及气道上皮细胞，若呈高表达则会诱发COPD气道高反应引起气道痉挛，加速患者机体炎症的进展；ST2作为IL-33的受体，可分为膜结合形态、变种形式及可溶性形式，而可溶性形式sST2能够与IL-33发生竞争性结合，抑制IL-33与ST2正常结合，阻滞Th2分化，生成IL-4、IL-5等炎症因子，所以IL-33/sST2轴表达异常会造成自身免疫疾病、炎症性疾病等[17]。通过多索茶碱联合盐酸氨溴索治疗能够显著改善患者机体内促炎因子/抗炎因子失衡状态，进而促使其恢复免疫功能[18]。本研究显示：两组治疗14 d后各炎症因子水平均显著降低，且试验组降低更明显(均$P<0.05$)。这表明盐酸氨溴索与多索茶碱联合治疗可显著缓解患者机体炎症反应，促进炎症损伤缓解。其主要原因为：多索茶碱对促炎因子及炎症因子有较强抑制作用，从而改善肺部病灶组织炎症环境，缓解气道高反应和炎症反应；氨溴索能够起到有效抗氧化、抑制炎症介质的效果，两者相结合可起到协同作用，提高抗炎效果[19-20]。本研究显示：试验组治疗总不良反应发生率较对照组低，充分体现联合用药的安全性。

综上所述，多索茶碱联合盐酸氨溴索治疗老年稳定期COPD患者疗效确切，能够改善肺功能，抑制血清IL-33/sST2轴表达水平，降低炎症因子水平，且不良反应小，安全可靠。但本研究所选样本量不足，且随访时间较短，今后应扩大样本量做长期研究加以验证。

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