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痰热清注射液对 COPD 患者血清 TGF-β 与 MMP-9 水平的影响 *

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摘要 目的：分析痰热清注射液对慢性阻塞性肺病(COPD)患者血清转化生长因子 -β(TGF-β)与基质金属蛋白酶 -9(MMP-9)水平的影响。**方法：**将 102 例 COPD 患者按随机数表法分作对照组与观察组，各 52 例。对照组予以常规治疗，观察组基于对照组加用痰热清注射液治疗，比较两组治疗前后血清 TGF-β、MMP-9 水平，用力肺活量 (FVC)、1s 用力呼气容积 (FEV1)，二氧化碳分压($PaCO_2$)、氧分压(PaO_2)，$CD4^+$、$CD8^+$、$CD4^+/CD8^+$，证候积分，临床疗效及不良反应的发生情况。**结果：**治疗后，观察组血清 TGF-β、MMP-9 水平、$PaCO_2$、证候积分均显著低于对照组，PaO_2、$CD4^+$、FVC、FEV1、$CD4^+/CD^+$、治疗总有效率均显著高于对照组(P<0.05)。两组药物副反应的发生情况比较差异无统计学意义(P>0.05)。**结论：**痰热清注射液可有效降低 COPD 患者血清 TGF-β 及 MMP-9 水平，并改善患者动脉血气、肺功能及免疫功能。

关键词：慢性阻塞肺疾病；痰热清注射液；转化生长因子 -β；基质金属蛋白酶 -9

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Effect of Tanreqing Injection on Serum Levels of TGF-β and MMP-9 of Patients with COPD*

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ABSTRACT Objective: To analyze the effect of tanreqing injection on the serum levels of transforming growth factor-β (TGF-β) and matrix metalloproteinases-9 (MMP-9) of patients with chronic obstructive pulmonary disease (COPD). **Methods:** 102 patients with COPD were divided into the control group and the observation group according to random number table method, 52 cases in each group. The control group was treated with routine therapy, and the observation group was treated with Tanreqing injection based on the control group. The serum TGF-β, MMP-9 levels, forced vital capacity (FVC), 1s forced expiratory volume (FEV1), partial pressure of carbon dioxide ($PaCO_2$),oxygen partial pressure (PaO_2), $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, syndrome integral, clinical efficacy and incidence of side effects were observed and compared between the two groups. **Results:** After treatment, the serum TGF-β, MMP-9 levels, $PaCO_2$ and syndrome integral of observation group were significantly lower than those of the control group, the PaO_2, $CD4^+$, FVC, FEV1, $CD4^+/CD8^+$ and the clinical efficacy of observation group were obviously higher than those of the control group (P<0.05). There was no significant difference in the incidence of side effects between the two groups (P>0.05). **Conclusion:** Tanreqing injection could effectively reduce the serum levels of TGF-β and MMP-9, and improve the arterial blood gas, lung function and immune function in treatment of patients with COPD.

Key words: Chronic pulmonary obstruction pulmonary disease; Tanreqing injection; Transforming growth factor-β; Matrix metalloproteinases-9

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前言

慢性阻塞性肺病 (chronic obstructive pulmonary disease，COPD)作为一种肺部的破坏性疾病，气流受限且不全部可逆是其特征，且多呈进行性的发展，导致患者生活质量显著下降[1]。国外研究显示气道重塑是 COPD 的进展和转归主要因素，转化生长因子 -β(TGF-β)与基质金属蛋白酶 -9(MMP-9)可参与气道重塑，从而影响 COPD 患者的预后[2]。有关研究显示在抗感染、化痰、止咳、平喘等治疗基础上加用中医配方治疗可增加疗效[3]。痰热清注射液具有祛痰镇惊、清热消毒等功效，已广泛应用于 COPD 治疗，但其作用机制尚不完全清楚[4]。本研究主要探讨了痰热清注射液对 COPD 患者血清 TGF-β 与 MMP-9 水平的影响。

1 资料与方法

1.1 一般资料

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选择我院 2014 年 6 月 ~2016 年 6 月收治的 102 例 COPD 患者为研究对象，患者及家属均签署知情同意书，且经过医院伦理委员会许可，按随机数表法分组。对照组 27 例男性，24 例女性，年龄 48~74 岁，平均(68.23± 1.57)岁。观察组 23 例男性，28 例女性，年龄 46~75 岁，平均(67.41± 1.52)岁。两组基线资料比较差异无统计学意义(P>0.05)，有可比性。

1.2 入选与排除标准

纳入标准[5]：① 符合 COPD 西医诊断标准：慢性咳痰、咳嗽比气流受限出现的时间早，第 1 秒用力呼气容积 / 用量肺活量在 0.7 以下、气流存在受限、无法全部逆转，肺部 X 线胸片提示可有肺部紊乱、增粗等变化、也可见肺气肿；② 经中医诊断为痰热阻肺证：痰多、黏稠，且色黄，身热，口渴、苔黄舌红，脉数滑；③ COPD 稳定期；④ 无其他呼吸系统病变。排除标准：① 肿瘤、糖尿病、肺结核等慢性消耗疾病；② 血液系统异常；③ 过敏体质；④ 近期接受过免疫抑制剂治疗；⑤ 急性创伤或者感染。

1.3 治疗方法

对照组采用维持电解质平衡、祛痰、平喘、营养支持、抗感染、持续低流量氧疗等常规治疗。观察组基于对照组加用痰热清注射液治疗，将 20 mL 痰热清注射液(来自广西仁源药业有限公司，10 mg/ 支，国药准字：Z20030054，批号：140511)溶于 250 mL 生理盐水，以静脉滴注给药，滴注速度控制在 40 滴 /min 以下，每天 1 次。两组均持续 14 天用药，于治疗结束时评估临床疗效，并记录期间的不良反应。

1.4 观察指标

1.4.1 指标检测 于用药前后抽取患者各 2 mL 空腹动静脉血，分离血清后待检。TGF-β 按酶联免疫双抗体夹心法测定，MMP-9 按电化学发光测定。$CD4^+$、$CD8^+$ 按流式细胞术测定。使用肺功能仪检测用力肺活量 (FVC)、1s 用力呼气容积(FEV1)。使用动脉血气分析仪检测二氧化碳分压 ($PaCO_2$)、氧分压 (PaO_2)。

1.4.2 证候积分[6] 选择 COPD 痰热阻肺证中脉滑数、苔红、发热、咳痰、咳嗽、口渴 6 个症状，按体征及症状程度分为“重度、中度、轻度、无”4 个级别，并分别计作 3 分、2 分、1 分、0 分，病情程度与分数呈正相关。

1.4.3 临床疗效[7] 临床体征及症状完全消失，证候积分下降在 95%以上即临床控制；临床体征及症状显著缓解，证候积分下降在 70%以上即显效；临床体征及症状有一定缓解，证候积分下降在 30%以上即好转；临床体征及症状较治疗前无变化甚至加剧，证候积分降低在 30%以下即无效。临床控制、显效及好转均视作有效。

1.5 统计学分析

选用 SPSS18.0 行数据统计，计量资料用($\bar{x}\pm s$)表示，用 t 检验比较，计数资料用[(n)%]表示，用 χ^2 检验比较，等级资料用秩和检验，P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者治疗前后血清 TGF-β、MMP-9 水平比较

治疗前，两组血清 TGF-β、MMP-9 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 TGF-β、MMP-9 水平均较治疗前显著降低，观察组降低更明显，组间比较差异有统计学意义(P<0.05)，见表 1。

表 1 两组患者治疗前后血清 TGF-β、MMP-9 水平的比较($\bar{x}\pm s$)

Table 1 Comparison of the serum TGF-β and MMP-9 levels between two groups before and after the treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=51)	Observation group(n=51)
TGF-β(ng/L)	Before treatment	99.54± 12.43	98.21± 13.50
	After treatment	74.23± 9.25#	67.80± 8.39*#
MMP-9(μg/L)	Before treatment	718.43± 102.57	720.86± 99.54
	After treatment	516.37± 73.70#	354.20± 44.25*#

Note: compared with the control group, * P<0.05; compared with before treatment, #P<0.05.

2.2 两组治疗前后 FVC、FEV1 的比较

治疗前，两组 FVC、FEV1 比较差异无统计学意义(P>0.05)；治疗后，两组 FVC、FEV1 均较治疗前显著上升，且观察组上升更明显，组间比较差异有统计学意义(P<0.05)，见表 2。

表 2 两组患者治疗前后 FVC、FEV1 的比较($\bar{x}\pm s$)

Table 2 Comparison of the FVC and FEV1 between two groups before and after the treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=51)	Observation group(n=51)
FVC(L)	Before treatment	2.23± 0.27	2.20± 0.28
	After treatment	2.53± 0.31#	2.71± 0.33*#
FEV1(L)	Before treatment	1.55± 0.19	1.56± 0.20
	After treatment	1.74± 0.21#	1.98± 0.24*#

Note: compared with the control group, * P<0.05; compared with before treatment, #P<0.05.

2.3 两组患者治疗前后 $PaCO_2$、PaO_2 的比较

治疗前，两组 $PaCO_2$、PaO_2 比较差异无统计学意义(P>0.05)；治疗后，两组 $PaCO_2$ 均较治疗前降低，两组 PaO_2 均较治疗前上升，观察组 $PaCO_2$、PaO_2 的改善更明显，组间比较差异有统

计学意义(P<0.05),见表 3。

表 3 两组患者治疗前后 $PaCO_2$、PaO_2 的比较($\bar{x}\pm s$)

Table 3 Comparison of the $PaCO_2$ and PaO_2 between two groups before and after the treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=51)	Observation group(n=51)
$PaCO_2$(mmHg)	Before treatment	57.63± 7.20	58.42± 7.32
	After treatment	48.65± 6.07#	43.20± 5.41‧#
PaO_2(mmHg)	Before treatment	76.33± 9.53	75.29± 9.42
	After treatment	82.41± 10.30#	87.90± 14.06‧#

Note: compared with the control group, ‧ P<0.05; compared with before treatment, #P<0.05.

2.4 两组患者治疗前后 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 的比较

治疗前，两组 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 比较差异无统计学意义(P>0.05)；治疗后，两组 $CD4^+$、$CD4^+/CD8^+$ 均较治疗前上升，且观察组显著高于对照组，两组 $CD8^+$ 均较治疗前明显降低，观察组明显低于对照组，组间比较差异有统计学意义(P<0.05)，见表 4。

表 4 两组患者治疗前后 $CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 的比较($\bar{x}\pm s$)

Table 4 Comparison of the $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ between two groups before and after the treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=51)	Observation group(n=51)
$CD4^+$(%)	Before treatment	25.87± 3.68	26.42± 3.30
	After treatment	32.11± 4.02#	38.60± 4.81‧#
$CD8^+$(%)	Before treatment	31.65± 3.95	32.27± 4.02
	After treatment	28.70± 3.59#	26.29± 3.28‧#
$CD4^+/CD8^+$	Before treatment	0.82± 0.10	0.81± 0.11
	After treatment	1.15± 0.14#	1.46± 0.18‧#

Note: compared with control group, ?P<0.05; compared with before treatment, #P<0.05.

2.5 两组患者治疗前后证候积分的比较

治疗前，两组证候积分比较差异无统计学意义(P>0.05)；治疗后，两组证候积分均较治疗前显著降低，观察组降低更明显，组间比较差异有统计学意义(P<0.05)，见表 5。

表 5 两组患者治疗前后证候积分的比较($\bar{x}\pm s$)

Table 5 Comparison of the syndrome integral between two groups before and after the treatment ($\bar{x}\pm s$)

Items	Time	Control group(n=51)	Observation group(n=51)
Syndrome integral(points)	Before treatment	8.21± 1.03	7.94± 0.99
	After treatment	5.15± 0.64#	3.21± 0.40‧#

Note: Compared with the control group, ‧ P<0.05; Compared with before treatment, #P<0.05.

2.6 两组临床疗效及不良反应发生情况的比较

观察组有效率为 96.08%，显著高于对照组，组间比较差异有统计学意义(P<0.05)，见表 6。用药期间，两组患者均未见显著不良反应，组间比较差异无统计学意义(P>0.05)。

表 6 两组患者临床疗效的比较[(例)%]

Table 6 Comparison of the clinical efficacy between two groups [(n)%]

Items	Control group(n=51)	Observation group(n=51)
Clinical control	12(23.53)	16(31.37)
Markedly	11(21.57)	21(41.18)
Better	18(35.29)	12(23.53)
Invalid	10(19.61)	2(3.92)
Effective rate	41(80.39)	49(96.08)?

Note: Compared with the control group, ‧ P<0.05; Compared with before treatment, #P<0.05.

3 讨论

COPD 是肺部常见疾病，可引起咳嗽、咯痰、呼吸困难、气短等临床表现，稳定期 COPD 以控制病情、提高肺功能、改善生活质量、减少病死率为治疗原则[8]。临床采用常规治疗，虽可缓解临床症状，但仍无法从本质上改善[9]。COPD 属中医学“喘证、痰饮、肺胀”等范畴，肺感外邪是其主要病机，痰浊为肺胀之契机，肺为娇脏，邪可攻正，邪气入里，致肺宣降所失，津液化痰，邪热至肺，使肺络所伤，阴津热灼，继而为痰[10,11]。治疗应以化痰解痉、清热解毒，痰热清选用黄芪作为君药，其性寒、味苦，入大肠、胃、肺经，可起泻火驱毒、祛热化湿之功；山羊角、熊胆粉作为臣药，二者可起清热解毒、养肝熄风、化痰除痉之功，金银花可解表宣肺、清热解毒；连翘可消结散肿、化热驱毒[12]。诸药配伍可共奏解毒、祛热、化痰之功。现代研究发现痰热清注射液可起到抗惊厥、解热、消炎、改善动脉血气、增强免疫功能等多种药物学作用[13]。

气道炎症及重塑是 COPD 的主要病变特点，细胞外基质是保持器官组织正常的关键，其沉积与降解失衡可引起气道壁结构失常、肺实质及间质增生、破坏，基质金属蛋白酶可介导细胞外基质的降解，从而参与气道病变[14,15]。MMP-9 可于内皮细胞、中性粒细胞、单核细胞等表达，可调控细胞外基质的降解与重建，经纤溶酶或者自身催化激活，诱导肺泡的基质成分受到破坏，影响肺泡结构，导致肺部肿胀，并调节气道重塑，引起气流受限 [16,17]。有关研究显示 MMP-9 的合成释放与 TGF-β 有关，TGF-β 作为一种活性多肽具有系列生物学作用，能够调控多种细胞组织的分化、坏死[18]，参与机体纤维化、炎性反应等病理反应，其可诱导 MMP-9 合成，导致其过度表达，引起肺部组织纤维化 [19]。本研究结果显示痰热清治疗后 COPD 患者血清 MMP-9、TGF-β 水平显著降低，提示痰热清可缓解气道炎症，减轻气道重塑，利于控制疾病的进展。

COPD 患者因气道高反应性及气道炎症、呼吸道纤毛对痰液的清除能力下降、痰液分泌增多等使气道内的黏液分泌物增加，导致痰液黏稠、且增多[20]。同时，患者由于呼吸比较急促，痰液难以咯出，使气道感染及阻塞加剧，引起肺功能减弱，导致血液中氧气浓度降低，并引起二氧化碳潴留，进一步加剧病情[21,22]。国外研究显示 COPD 患者使用痰热清注射液治疗后肺功能及血气分析指标均得到明显改善，可能与痰热清利于支气管痉挛的解除，缓解其黏膜水肿，提高呼吸道的清洁能力，促进肺部通气功能的改善，促进动脉血气的恢复有关[23,24]。有研究显示 CODP 患者多伴不同程度的免疫功能低下，其中细胞免疫功能改变最为明显，T 淋巴细胞亚群失衡，引起免疫功能出现紊乱[25]。$CD4^+$ 及 $CD8^+$ 为 T 淋巴细胞的不同亚型，其比例平衡是免疫功能正常的核心，$CD4^+$ 减少可引起 B 淋巴细胞等功能降低，导致免疫功能减弱，$CD8^+$ 过度表达可诱导机体出现损伤[26]。本研究结果显示痰热清治疗后 $CD4^+$、$CD4^+/CD8^+$ 显著上升，并下调 $CD8^+$ 表达，提示痰热清可纠正机体细胞免疫功能的平衡，使机体对疾病的抵抗能力增强。同时，本研究结果显示痰热清治疗后证候积分显著降低，且有效率明显高于常规治疗者，证实使用痰热清治疗可促进临床表现的改善，增强疗效，使患者生活质量得到提高。此外，两组用药期间均未见明显不良反应，提示其安全性较高。

综上所述，痰热清注射液可有效降低 COPD 患者血清 TGF-β 及 MMP-9 水平，并改善患者动脉血气、肺功能及免疫功能。

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