doi: 10.13241/j.cnki.pmb.2017.15.018

卡介菌多糖核酸对慢性阻塞性肺疾病患者炎症因子水平及免疫功能的影响 *

冯思芳 陈天君△ 阳 甜 李 洋 权红丽 王沙沙

（西安交通大学第一附属医院 呼吸与危重症医学科 陕西 西安 710061）

摘要 目的:分析卡介菌多糖核酸对慢性阻塞性肺疾病患者炎症因子水平及免疫功能的影响。**方法:**随机将 110 例慢性阻塞性肺疾病患者分为对照组与观察组,每组 55 例。对照组采用常规治疗,观察组在常规治疗基础上加用卡介菌多糖核酸治疗,比较两组临床疗效,血清单核细胞样受体 4(TLR4)、白细胞介素 -8(IL-8)、肿瘤坏死因子 -α(TNF-α)、脂质过氧化物(LPO)、超氧化物歧化酶(SOD)、金属蛋白抑制 1(TIMP-1)及金属蛋白酶 -9(MMP-9)水平,$CD4^+$、$CD4^+/CD8^+$、$CD8^+$ 水平,第 1 秒用力呼气容积(FEV1)、肺活量(FVC)。**结果:**观察组总有效率为 96.86%,显著高于对照组 81.82%,差异有统计学意义(P<0.05)。治疗后,观察组血清 TLR4、IL-8、TNF-α、LPO、TIMP-1、MMP-9、HMGB1 水平、FEV1、FVC 及 $CD8^+$ 低于对照组,SOD 水平、$CD4^+$、$CD4^+/CD8^+$ 高于对照组,差异均有统计学意义(P<0.05)。**结论:**卡介菌多糖核治疗慢性阻塞性肺疾病的临床疗效肯定,可选择性减轻炎症反应并改善免疫功能。

关键词:慢性阻塞性肺疾病;卡介菌多糖核酸;炎症因子;免疫功能

中图分类号:R563 **文献标识码:**A **文章编号:**1673-6273(2017)15-2873-04

Effect of Bacillus Calmette-guerin Polysaccharide Nucleic Acid on the Inflammatory Factors and Immune Functions of Patients with Chronic Obstructive Pulmonary Disease*

FENG Si-fang, CHEN Tian-jun△, YANG Tian, LI Yang, QUAN Hong-li, WANG Sha-sha

(Department of respiratory and critical care medicine, the First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, Shaanxi, 710061, China)

ABSTRACT Objective: To analyze the effect of bacillus calmette-guerin polysaccharide nucleic acid on the inflammatory factor levels and immune function of patients with chronic obstructive pulmonary disease. **Methods:** 110 cases of chronic obstructive pulmonary disease patients were divided into the control group and the observation group according to the random number table method, 55 cases in the control group was given conventional treatment, while the observation group was given bacillus calmette-guerin polysaccharide nucleic acid on the basis of control group, the clinical curative effect, monocyte like receptor 4 (TLR4), serum interleukin 8 (IL-8), tumor necrosis factor-α(TNF-α), lipid peroxide (LPO) and superoxide dismutase (SOD), metal protein-1 (TIMP-1) and metalloproteinases-9 (MMP-9), $CD4^+$, $CD4^+/CD8^+$, $CD8^+$, forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) between two groups were compared. **Results:** The total effective rate of observation group was 96.86%, which was significantly higher than that of control group (81.82%, P<0.05). After treatment, the TLR4, IL-8, serum TNF-α, LPO, MMP-9 and TIMP-1, HMGB1 level, FEV1 and FVC and $CD8^+$ of observation group were lower than those of the control group, the SOD level, $CD4^+$, $CD4^+/CD8^+$ of observation group were higher than those of the control group (P<0.05). **Conclusion:** Polysaccharide core of bacillus calmette-guerin had good clinical efficacy in the treatment of chronic obstructive pulmonary disease, which could selectively reduce the inflammatory response and improve the immune function.

Key words: Chronic obstructive pulmonary disease; Bacillus calmette-guerin polysaccharide nucleic acid; Inflammatory factor; Immune function

Chinese Library Classification(CLC): R563 Document code: A

Article ID: 1673-6273(2017)15-2873-04

前言

慢性阻塞性肺疾病表现为反复性、进行性缓慢发展,可引起系列并发症,严重影响患者的生活质量[1,2]。相关研究表明外周血高迁移率族蛋白 1(HMGB1)、白细胞介素 -8(IL-8)、单核细胞样受体 4(TLR4)及肿瘤坏死因子 -α(TNF-α)等炎性因子在慢性阻塞性肺疾病发病中起到重要作用[3]。另有研究表示免疫功能降低是慢性阻塞性肺疾病的又一主要诱因[4]。卡介菌多糖核酸是免疫调节的新型药物,能够使患者的免疫功能得到有效改善[5]。本研究旨在分析卡介菌多糖核酸对慢性阻塞性肺疾病患

* 基金项目:陕西省科技攻关项目(2009K11-15)

△ 通讯作者:陈天君(1979-),男,博士,副主任医师,研究方向:肺癌的基础与临床研究

(收稿日期:2016-11-30 接受日期:2016-12-20)

者炎症因子水平及免疫功能的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择 2014 年 5 月 ~2016 年 5 月于我院诊治的 110 例慢性阻塞性肺疾病患者,均符合《慢性阻塞性肺疾病诊治指南》的诊断有关标准[6]:第 1 秒用力呼气容积 / 用量肺活量低于 0.7、且伴气流受限、无法全部逆转;慢性咳痰、咳嗽比气流受限出现的时间早;肺部 X 线胸片提示可有肺部紊乱紊乱、增粗等变化、也可见肺气肿。纳入疾病稳定期,心肝肾等主要脏器无严重异常,无恶性肿瘤,无肺部其他疾病。排除近期有免疫抑制剂使用史,急性创伤或者感染,自身免疫系统障碍者。对照组有 29 例男性,有 26 例女性;年龄 50~75 岁,平均(67.42± 1.13)岁;病程 3~14 年,平均(8.63± 1.07)年。观察组有 31 例男性,有 24 例女性;年龄 52~78 岁,平均(68.14± 1.18)岁;病程 3~16 年,平均(8.75± 1.12)年。两组一般资料比较无明显差异(P>0.05),有比较性。

1.2 治疗方法

对照组予以平喘、祛痰、抗感染、维持电解质平衡、持续低流量氧疗等常规治疗。观察组在常规治疗后结合卡介菌多糖核酸治疗,肌肉注射 0.35 mg 卡介菌多糖核酸(大同市云岗制药有限公司,1 mL/ 支,20140426)持续用药 4 周。

1.3 疗效评估

症状和体征消失,未见实验室指标异常,生活无需外界帮助即显效;症状及体征显著减轻,可见部分实验室指标异常即好转;症状和体征无改变、甚者加重即无效。显效 + 好转 = 总有效[6]。

1.4 指标测定

1.4.1 炎症因子 抽取患者用药前及用药结束时外周静脉血 3 mL,常规处理血液标本。使用实时荧光定量法检测 TLR4;使用酶联免疫吸附法检测 IL-8、TNF-α 及 HMGB1; 使用化学比色法脂质过氧化物(LPO)及超氧化物歧化酶(SOD)水平;使用化学比色法检测金属蛋白抑制 1 (TIMP-1) 及金属蛋白酶 -9 (MMP-9)。

1.4.2 免疫功能 使用流式细胞术检测 $CD4^+$、$CD8^+$。

1.4.3 肺功能 使用肺功能仪检测第 1 秒用力呼气容积 (FEV1)、肺活量(FVC)。

1.5 统计学分析

选择 SPSS18.0 行数据统计, 计量资料用均数± 标准差($\bar{x}$± s)表示,用 t 检验比较,计数资料用[(n)%]表示,用 x^2 检验比较,等级资料用秩和检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组总有效率为 96.86%,显著高于对照组(81.82%),两组比较差异有统计学意义(P<0.05),见表 1。

表 1 两组临床疗效比较[例(%)]

Table 1 Comparison of the clinical curative effect between two groups[n(%)]

Groups	n	Markedly	Better	Invalid	Total effective rate
Control group	55	18(32.73)	27(49.09)	10(18.18)	45(81.82)
Observation group	55	27(49.09)	26(47.27)	2(36.36)	53(96.36)
P			0.020		0.014

2.2 两组患者治疗前后肺功能比较

治疗前,两组肺功能指标比较差异无统计学意义(P>0.05);治疗后,两组肺功能均较治疗前改善,观察组改善更明显,两组比较差异有统计学意义(P<0.05),见表 2。

表 2 两组患者治疗前后肺功能比较($\bar{x}$± s)

Table 2 Comparison the lung function between two groups before and after treatment($\bar{x}$± s)

Groups	n	FVC(L)		FEV1(L)		FEV1/FVC(%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	55	2.09± 0.36	2.26± 0.38	1.07± 0.21	1.29± 0.24	1.10± 0.13	1.13± 0.15
Observation group	55	2.10± 0.34	2.49± 0.43	1.08± 0.20	1.50± 0.28	1.11± 0.15	1.54± 0.21
P		0.881	0.003	0.798	0.000	0.709	0.000

2.3 两组患者治疗前后血清 TLR4、IL-8、TNF-α 及 HMGB1 水平比较

治疗前, 两组血清 TLR4、IL-8、TNF-α 及 HMGB1 水平比较差异无统计学意义(P>0.05);治疗后,两组血清 TLR4、IL-8、TNF-α 及 HMGB1 水平均均显著低于治疗前,且观察组明显低于对照组,两组比较差异有统计学意义(P<0.05),见表 3。

2.4 两组患者治疗前后免疫功能比较

治疗前, 两组 $CD4^+$、$CD4^+/CD8^+$、$CD8^+$ 比较差异均无统计学意义(P>0.05);治疗后,对照组 $CD4^+$、$CD4^+/CD8^+$、$CD8^+$ 无改善,观察组 $CD4^+$、$CD4^+/CD8^+$ 高于治疗前,$CD8^+$ 低于治疗前,两组比较差异有统计学意义(P<0.05),见表 4。

2.5 两组患者治疗前后血清 LPO、SOD 水平比较

治疗前,两组血清 LPO、SOD 水平差异无统计学意义(P>0.05);治疗后,两组血清 LPO 水平均低于治疗前,且观察组低于对照组,两组血清 SOD 水平均高于治疗前,且观察组高于对照组,两组比较差异有统计学意义(P<0.05),见表 5。

2.6 两组患者治疗前后血清 TIMP-1、MMP-9 水平比较

治疗前, 两组血清 TIMP-1、MMP-9 水平比较差异无统计学意义(P>0.05);治疗后,两组血清 TIMP-1、MMP-9 水平均较治疗前显著降低,且观察组明显低于对照组,差异有统计学意

义(P<0.05),见表 6。

表 3 两组患者治疗前后血清 TLR4、IL-8、TNF-α 及 HMGB1水平比较($\bar{x}\pm$ s)

Table 3 Comparison of the serum levels of TLR4, IL-8, TNF-α and HMGB1 between two groups before and after treatment($\bar{x}\pm$ s)

Groups	n	TLR4(× 10^5)		IL-8(ng/L)		TNF-α(μg/L)		HMGB1(μg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	55	5.38± 0.87	3.44± 0.56	5.72± 0.82	4.46± 0.80	68.43± 10.30	38.79± 6.45	311.56± 12.40	187.60± 10.15
Observation group	55	5.42± 0.98	1.34± 0.16	5.70± 0.84	3.25± 0.73	69.11± 10.19	27.59± 5.40	313.58± 12.30	127.63± 9.51
P		0.821	0.000	0.899	0.000	0.728	0.000	0.392	0.000

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

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

Groups	n	$CD4^+$(%)		$CD8^+$(%)		$CD4^+/CD8^+$(%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	55	32.73± 3.30	33.69± 4.12	29.54± 2.61	28.96± 2.50	1.10± 0.13	1.13± 0.15
Observation group	55	32.68± 3.21	45.41± 5.06	29.35± 2.52	26.25± 1.89	1.11± 0.15	1.54± 0.21
P		0.936	0.000	0.698	0.000	0.709	0.000

表 5 两组患者治疗前后血清 LPO、SOD 水平比较($\bar{x}\pm$ s)

Table 5 Comparison of the serum levels of LPO, SOD between two groups before and after treatment

Groups	n	LPO(mmol/mL)		SOD(Nu/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	3.67± 0.68	3.19± 0.59	22.30± 4.17	26.30± 4.40
Observation group	55	3.65± 0.64	2.60± 0.52	22.16± 4.13	30.75± 4.81
P		0.874	0.000	0.859	0.000

表 6 两组患者治疗前后血清 TIMP-1、MMP-9 水平比较($\bar{x}\pm$ s)

Table 6 Comparison levels of the serum TIMP-1, MMP-9 levels between two groups before and after treatment($\bar{x}\pm$ s)

Groups	n	TIMP-1(μg/L)		MMP-9(μg/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	237.50± 46.20	204.89± 40.21	130.59± 20.48	92.73± 16.81
Observation group	55	235.41± 45.18	176.19± 38.60	132.60± 20.83	68.94± 14.70
P		0.810	0.000	0.610	0.000

3 讨论

慢性浸润性炎症、肺血管损伤等反应能够使细胞外基质出现增加,诱导平滑肌细胞形成增生,导致管腔发生狭窄,增厚肺小动脉,进而引起慢性阻塞性肺疾病的发生[7,8]。慢性阻塞性肺疾病尚无特定治疗手段,目前治疗仍以改善患者生活质量,症状缓解为主[9]。近年来研究显示免疫反应是慢性阻塞性肺疾病的重要发病机制,为临床提供了新的治疗方向[10]。机体正常免疫功能状态的维持需要 T 细胞亚群的互相作用,$CD4^+$ 能够起到辅助调节作用,抑制病毒细胞的复制和变异,进一步避免免疫损伤发展;$CD8^+$ 有细胞毒性效应,能够导致细胞功能产生紊乱,若 $CD4^+/CD8^+$ 比值降低,则可使免疫功能产生抑制。

炎症反应能够使系列肺结构细胞和相关炎症细胞激活,于慢性阻塞性肺疾病发生期间发挥关键作用[11]。TLR4 对病原体相关分子模式有识别作用,进而导致细胞内传导信号通路激活,诱导机体释放炎症因子,使患者病情加重[12,13]。IL-8 作为白细胞重要的趋化因子,能够结合中性粒细胞的特定受体,诱导其趋化并变形,导致组织受损,使气道壁产生增厚,引起气流阻塞[14,15]。TNF-α 能够利于炎症介质的浸润和游离,导致肺功能受损,同时也可使中性粒细胞的分解能力,造成炎症反应加剧,诱导组织产生纤维化,促进血管新生[16,17]。HMGB1 作为一种非 DNA 蛋白,与其他炎症介质结合后能够导致炎症反应加强,形成内分泌分复杂调节网络[18,19]。

卡介菌多糖核酸是菌体多糖之一,为免疫调节的新型药物。本研究显示卡介菌多糖核酸治疗后总有效率显著显著高于常规治疗,表明其临床效果好,能够控制病情,减轻患者痛苦。同时,卡介菌多糖核酸治疗后 TLR4、IL-8、TNF-α 及 HMGB1 水平更低,表明其可有抑制炎症因子的分泌,使炎症反应对于肺组织造成的损伤降低;此外,卡介菌多糖核酸治疗后免疫功能改善更明显,表明其可有效纠正免疫功能紊乱。

有研究显示慢性阻塞性肺疾病与氧化 - 抗氧化失衡有着密切联系,发病期间因细菌感染使中性粒细胞释放,增加 LPO

生成,导致支气管出现黏膜水肿,还可使气道狭窄[20]。若机体内SOD无法有效清除自由基及LPO时,则可导致损伤,加重患者呼吸道症状。本研究显示,卡介菌多糖核酸治疗后LPO水平显著降低,且SOD明显高于治疗前,表明其可恢复机体氧化-抗氧化平衡,保持机体形成一个正常代谢。TIMP-1及MMP-9的能够保持气道的动态平衡,TIMP-1能够修复受损组织,但浓度过高时又可促进表皮细胞及平滑肌细胞出现增殖;MMP-9能够导致肺泡壁的基底膜发生降解,诱导肺气肿。本研究显示卡介菌多糖核酸治疗后TIMP-1及MMP-9更低,表明其可抑制MMPs的过表达,减轻气道阻力。同时,卡介菌多糖核酸治疗后肺功能改善更明显,表明其可改善肺通气状态,提高肺功能。

综上所述,卡介菌多糖核治疗慢性阻塞性肺疾病的临床疗效肯定,可选择减轻炎症反应并改善免疫功能。

参考文献(References)

[1] Hirai T. Osteoporosis in chronic obstructive pulmonary disease [J]. Clin Calcium, 2016, 26(10): 1393-1398

[2] Dudgeon D, Baracos VE. Physiological and functional failure in chronic obstructive pulmonary disease, congestive heart failure and cancer: a debilitating intersection of sarcopenia, cachexia and breathlessness[J]. Curr Opin Support Palliat Care, 2016, 16(3): 236-241

[3] Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease [J]. J Allergy Clin Immunol, 2016, 138(1): 16-27

[4] Il'nyts'kyĭ RI. Immunological reactivity and correction of immunological disorders by biological medicines in patients with chronic obstructive pulmonary disease exacerbations [J]. Lik Sprava, 2014, 7(8): 22-27

[5] Zhang Yan, Zhang Ceng, Wang Na, et al. Effects of polysaccharide nucleic acid of BCG on immune function in patients with chronic obstructive pulmonary disease [J]. China Pharmacy,2011, 22 (36): 3394-3395

[6] Chinese medical association respiratory neurology, Chronic obstructive pulmonary disease group. The diagnosis and treatment guidelines of chronic obstructive pulmonary disease (2013 edition) (a) [J]. Chinese tuberculosis and respiratory journal, 2013, 36 (4): 484-491

[7] Chen X, Cao J, Chen BY. Interleukin-17 expression and clinical significance in the lung tissue of patients with stable chronic obstructive pulmonary disease [J]. Zhonghua Yi Xue Za Zhi, 2016, 96 (26): 2086-2090

[8] Tan DB, Amran FS, Teo TH, et al. Levels of CMV-reactive antibodies correlate with the induction of CD28 (null) T cells and systemicinflammation in chronic obstructive pulmonary disease (COPD)[J]. Cell Mol Immunol, 2016, 13(4): 551-553

[9] Campo G, Pavasini R, Biscaglia S, et al. Overview of the pharmacological challenges facing physicians in the management of patients with concomitant cardiovascular disease and chronic obstructive pulmonary disease [J]. Eur Heart J Cardiovasc Pharmacother, 2015, 15 (3): 205-211

[10] Young RP, Hopkins RJ, Marsland B. The Gut-Liver-Lung Axis. Modulation of the Innate Immune Response and Its Possible Role in Chronic Obstructive Pulmonary Disease[J]. Am J Respir Cell Mol Biol, 2016, 54(2): 161-169

[11] Abd El-Kader SM, Al-Jiffri OH, Al-Shreef FM. Plasma inflammatory biomarkers response to aerobic versus resisted exercise training for chronic obstructive pulmonary disease patients [J]. Afr Health Sci, 2016, 6(2): 507-515

[12] Xie Yaun-yuan, Yang Dan-fen. Study on the Expressions of TLR2, TLR4 in Peripheral Blood Mononuclear Cells and Its Correlation with the Inflammglammactory Factors Levels of the elderly Patients with COPD [J]. Modern Journal of Laboratory Medicine, 2015, 30(4): 80-83

[13] Zhang Xin-wen, Cong Jin-peng, Ding Lei, et al. Role of TLR -4 and BMP -2 Expression in Pulmonary Vascular Remodeling in Patients with Chronic Obstructive Pulmonary Disease [J]. Chinese Journal of General Practitioners, 2014, 17(36): 4298-4301

[14] Gu Fu-gen, Ding Qun-li. The expression of serum IL-8, TNF-α, CRP in stable chronic obstructive pulmonary disease, and the relationship between lung function [J]. Modern Practical Medicine, 2015, 27(8): 1021-1023

[15] Ji Ying, Wang Xin-jie. The changes and significance of serum IL-8, TNF-α in chronic obstructive pulmonary disease [J]. Medical Review, 2012, 18(8): 1249-1250

[16] Kochetkova EA, Nevzorova VA, Ugai LG, et al. The Role of Tumor Necrosis Factor Alpha and TNF Superfamily Members in Bone Damage in Patients with End-Stage Chronic Obstructive Lung Disease Prior to Lung Transplantation[J]. Calcif Tissue Int, 2016, 99(6): 578-587

[17] Liu XJ, Bao HR, Zeng XL, et al. Effects of resveratrol and genistein on nuclear factor κ B, tumor necrosis factor α and matrix metalloproteinase 9 in patients with chronic obstructive pulmonary disease [J]. Mol Med Rep, 2016, 13(5): 4266-4272

[18] Ko HK, Hsu WH, Hsieh CC, et al. High expression of high-mobility group box 1 in the blood and lungs is associated with the development of chronic obstructive pulmonary disease in smokers [J]. Respirology, 2014, 9(2): 253-261

[19] Wang Chang-ming, Jiang Ming, Wng Hui-juan, et al. The correlation between the expression of HMGBl and the airway remodeling, pulmonary vascular reCOnStrUCtiOn in rats with chronic obstructire pulmonary disease and clinicaI significance [J]. Journal of chongqing medical university, 2012, 37(2): 114-117

[20] Xu Lin, Zhang Cheng, Wang Na, et al. The effects of Bacillus calmette-guerin polysaccharide nucleic acid on humoral immunity and peripheral blood interleukin-8 and tumor necrosis factor-αin in patients with chronic obstructive pulmonary disease [J]. West China Journal of Medicine, 2015, 30(1): 1-5