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利福布汀胶囊联合莫西沙星治疗耐多药肺结核的疗效 及对炎症因子和 T 细胞亚群的影响 *

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摘要 目的:探讨利福布汀胶囊联合莫西沙星治疗耐多药肺结核的疗效及对炎症因子和 T 细胞亚群的影响。**方法:**选取 2016 年 6 月~2018 年 6 月期间我院收治的耐多药肺结核患者 110 例,上述患者根据随机数字表法分为对照组(n=55)和研究组(n=55),对照组患者予以利福布汀胶囊联合左氧氟沙星治疗,研究组则给予利福布汀胶囊联合莫西沙星治疗,比较两组患者疗效、炎症因子和 T 细胞亚群水平,记录两组治疗期间不良反应发生情况。**结果:**研究组治疗 12 个月后、治疗 18 个月后病灶吸收率、空洞闭合率、痰菌转阴率均高于对照组($P<0.05$)。两组治疗 18 个月后肿瘤坏死因子- α (TNF- α)、白介素-6(IL-6)、C 反应蛋白(CRP)均较治疗前降低,且研究组低于对照组($P<0.05$)。两组患者治疗 18 个月后 CD4⁺/CD8⁺、CD4⁺较治疗前升高,且研究组高于对照组($P<0.05$),CD8⁺较治疗前降低,且研究组低于对照组($P<0.05$)。两组不良反应发生率比较无差异($P>0.05$)。**结论:**利福布汀胶囊联合莫西沙星治疗耐多药肺结核,疗效显著,可有效改善炎症因子和 T 细胞亚群水平,且安全性较好,临床应用价值较高。

关键词:利福布汀胶囊;莫西沙星;耐多药肺结核;疗效;炎症因子;T 细胞亚群

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The Effect of Rifabutin Capsule Combined with Moxifloxacin in the Treatment of Multidrug Resistant Tuberculosis and Its Effect on Inflammatory Factors and T Cell Subsets*

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ABSTRACT Objective: To investigate the effect of rifabutin combined with moxifloxacin in the treatment of multidrug resistant tuberculosis and its effect on inflammatory factors and T cell subsets. **Methods:** From June 2016 to June 2018, 110 multidrug resistant tuberculosis patients in our hospital were selected. The patients were divided into control group (n = 55) and study group (n = 55) according to the random number table method. The patients in the control group were treated with rifabutin capsule combined with levofloxacin, while those in the study group were treated with rifabutin capsule combined with moxifloxacin. The curative effect, inflammatory factors and T cell subsets levels of the two groups were compared. The adverse reactions of the two groups were recorded during the treatment. **Results:** The absorption rate of focus, the rate of cavity closure and the negative rate of sputum bacteria in the study group at 12 months after treatment and 18 months after treatment were higher than those in the control group ($P<0.05$). 18 months after treatment, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP) were lower than those before treatment, and the study group was lower than control group ($P<0.05$). 18 months after treatment, CD4⁺/CD8⁺ and CD4⁺ in two groups were higher than those before treatment, and the study group was higher than those control group ($P<0.05$). CD8⁺ was lower than before treatment, and that in the study group was lower than that in the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Rifabutin capsule combined with moxifloxacin is effective in the treatment of multidrug resistant tuberculosis. It can effectively improve the inflammatory factors and T cell subsets, and has good safety, and high clinical application value.

Key words: Rifabutin capsule; Moxifloxacin; Multidrug resistant tuberculosis; Efficacy; Inflammatory factors; T cell subsets

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前言

肺结核是目前死亡率较高的主要传染病之一,而耐多药肺结核是指对包括异烟肼、利福平在内的两种或两种以上药物产生耐药性的肺结核类型,由于耐药性的存在其具有病死率高、治愈率低、传染危害大等特征,已成为临床肺结核治疗的难点^[1-3]。近年来随着抗菌药物的滥用,加上部分初诊患者未按规定用药,致使耐多药肺结核的患者数量逐年递增^[4]。据以往数据统计^[5],我国肺结核患者数量居世界第二位,其中耐多药肺结核占新发肺结核病例的27.8%。利福布汀胶囊是利福霉素的螺旋哌啶衍生物,常将其用于耐多药肺结核的治疗中,但疗效并不十分理想^[6,7]。近年来有研究证实喹诺酮类抗生素利于对抗耐多药肺结核。莫西沙星作为喹诺酮类抗生素的代表药物,抗菌谱广,抗菌活性强^[8]。鉴于此,本研究通过对我院收治的部分耐多药肺结核患者给予利福布汀胶囊联合莫西沙星治疗,疗效显著,整理如下。

1 资料与方法

1.1 一般资料

选取2016年6月~2018年6月期间我院收治的110例耐多药肺结核患者,纳入标准:(1)诊断标准参考《肺结核诊断和治疗指南》^[9];(2)经胸部CT检查确定患者肺部存在结核病变,经结核分枝杆菌罗氏培养检查确诊为耐多药肺结核;(3)患者及其家属知情本研究且签署了同意书;(4)对本次研究用药耐受者。排除标准:(1)合并自身免疫缺陷者;(2)合并恶性肿瘤者;(3)合并其他部位结核者;(4)合并高血压、糖尿病、高血脂等基础疾病者;(5)合并心肝肾等脏器功能障碍者;(6)合并其他真菌、细菌等病原菌感染。上述患者根据随机数字表法分为对照组($n=55$,利福布汀胶囊联合左氧氟沙星治疗)和研究组($n=55$,利福布汀胶囊联合莫西沙星治疗),对照组男34例,女21例,年龄38~73岁,平均 (49.26 ± 5.14) 岁;病程1~8年,平均 (4.32 ± 0.85) 年;病变肺叶:左肺18例,右肺20例,双肺17例;体质量指数 $20.6\sim 26.5\text{kg/m}^2$,平均 $(23.16\pm 0.92)\text{kg/m}^2$ 。研究组男32例,女23例,年龄37~72岁,平均 (50.13 ± 4.97) 岁;病程2~6年,平均 (4.21 ± 0.74) 年;病变肺叶:左肺20例,右肺21例,双肺14例;体质量指数 $20.8\sim 27.2\text{kg/m}^2$,平均 $(23.35\pm 0.87)\text{kg/m}^2$ 。两组一般资料比较无差异($P>0.05$),具有可比性。本研究经我院伦理委员会批准进行。

1.2 方法

两组患者均给予对乙胺丁醇、吡嗪酰胺、丙硫异烟胺等药物行基础治疗。在此基础上,对照组予以利福布汀胶囊(四川明欣药业有限责任公司,国药准字H20070296,规格:0.15g)治疗,口服,0.6g/次,2次/d;盐酸左氧氟沙星片(上海衡山药业有限公司,国药准字H20113346,规格:按 $\text{C}_{18}\text{H}_{20}\text{FN}_3\text{O}_4$ 计0.1g)治疗,口服,0.4g/次,2次/d。研究组患者则予以利福布汀胶囊治疗,口服,0.3g/次,1次/d;莫西沙星(广东东阳光药业有限公司,国药准字H20183246,规格:以莫西沙星计0.4g)治疗,口服,0.4g/次,1次/d。两组治疗过程中加用保肝药物,连续治疗18个月。

1.3 观察指标

(1)疗效评价^[10]:记录两组患者治疗6个月后、治疗12个月后、治疗18个月后的痰菌阴转率、病灶吸收率以及空洞改善率。痰菌阴转率:收集患者晨间痰与夜间痰标本,进行痰培养与痰涂片,痰涂片3次及痰培养检测为阴性,则认为是痰菌转阴。病灶吸收率:根据胸部CT观察。病灶吸收率=吸收率+显著吸收率。显著吸收:治疗18个月后病灶面积缩小 $>50\%$;吸收:治疗18个月后病灶面积缩小 $\leq 50\%$;不变:治疗18个月后病灶面积无明显改变;恶化:治疗18个月后病灶面积增加。空洞闭合率:根据胸部CT观察。闭合:治疗18个月后空洞出现闭合;缩小:治疗18个月后空洞直径缩小 $>50\%$;不变:治疗18个月后空洞直径缩小 $\leq 50\%$;增加:治疗18个月后空洞直径增大;空洞闭合率=缩小率+闭合率。(2)炎症因子、T细胞亚群:于治疗前、治疗18个月后采集所有患者清晨空腹静脉血6mL,经常规离心处理(离心半径13cm,3000r/min离心10min)分离上清液后,置于冰箱中(-40°C)待测。采用酶联免疫吸附法检测肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、白介素-6(Interleukin-6, IL-6)水平,采用免疫透射比浊法检测血清中C反应蛋白(C-reactive protein, CRP)水平,严格按照试剂盒(深圳晶美生物科技有限公司)说明书进行操作。采用FACSCalibur流式细胞仪(美国BD公司产)检测外周血T细胞亚群水平:CD4⁺、CD8⁺,并计算CD4⁺/CD8⁺。(3)安全性评价:记录两组不良反应。

1.4 统计学方法

采用SPSS25.0软件分析数据。计数资料以[n(%)]表示,行卡方检验。以均值 $\pm$ 标准差表示计量资料,行t检验。检验标准设为 $\alpha=0.05$ 。

2 结果

2.1 两组疗效比较

两组治疗6个月后痰菌转阴率、病灶吸收率、空洞闭合率比较无统计学差异($P>0.05$),研究组治疗12个月后、治疗18个月后病灶吸收率、空洞闭合率、痰菌转阴率均高于对照组($P<0.05$),详见表1。

2.2 两组血清炎症因子水平比较

两组治疗前IL-6、CRP、TNF- α 比较无统计学差异($P>0.05$),两组治疗18个月后IL-6、CRP、TNF- α 均较治疗前降低,且研究组低于对照组($P<0.05$),详见表2。

2.3 两组T淋巴细胞亚群水平比较

两组治疗前CD8⁺、CD4⁺、CD4⁺/CD8⁺比较无差异($P>0.05$),两组患者治疗18个月后CD4⁺/CD8⁺、CD4⁺较治疗前升高,且研究组高于对照组($P<0.05$),CD8⁺较治疗前降低,且研究组低于对照组($P<0.05$),详见表3。

2.4 两组不良反应发生率比较

两组不良反应发生率比较无差异($P>0.05$);详见表4。

3 讨论

肺结核临床主要表现为咳嗽、咯血、咳嗽、胸痛等症状,无明显肺部体征^[11]。近年来,全球肺结核的疫情有回升迹象,且临床使用抗结核药物不规范,增加了耐多药肺结核的发病率,其已成为临床上的一大治疗难点^[12-14]。由于耐多药肺结核患者病

表 1 两组患者疗效比较【例(%)】

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

Groups	Negative rate of sputum bacteria			Absorption rate of focus			Rate of cavity closure		
	6 months	12 months	18 months	6 months	12 months	18 months	6 months	12 months	18 months
	after treatment	after treatment	after treatment	after treatment	after treatment	after treatment	after treatment	after treatment	after treatment
Control group(n=55)	15(27.27)	22(40.00)	32(58.18)	17(30.91)	25(45.45)	34(61.82)	14(25.45)	24(43.64)	35(63.64)
Study group (n=55)	20(36.36)	34(61.82)	48(87.27)	23(41.82)	37(67.27)	50(90.91)	19(34.55)	37(67.27)	49(89.09)
χ^2	1.048	5.238	12.383	1.414	5.323	12.894	1.082	6.760	9.872
<i>P</i>	0.306	0.022	0.000	0.234	0.021	0.000	0.298	0.009	0.002

表 2 两组血清炎症因子水平比较($\bar{x} \pm s$)Table 2 Comparison of serum inflammatory factors between the two groups($\bar{x} \pm s$)

Groups	IL-6($\mu\text{g/L}$)		CRP(mg/L)		TNF- α ($\mu\text{g/L}$)	
	Before treatment	18 months after treatment	Before treatment	18 months after treatment	Before treatment	18 months after treatment
Control group (n=55)	283.78 $\pm$ 32.37	196.42 $\pm$ 27.33*	42.56 $\pm$ 5.39	28.36 $\pm$ 5.32*	184.53 $\pm$ 29.65	143.51 $\pm$ 36.84*
Study group(n=55)	281.72 $\pm$ 27.38	142.46 $\pm$ 30.41*	41.91 $\pm$ 6.35	17.39 $\pm$ 4.35*	182.96 $\pm$ 35.72	96.82 $\pm$ 26.54*
<i>t</i>	0.360	9.788	0.579	11.839	0.251	19.654
<i>P</i>	0.719	0.000	0.564	0.000	0.802	0.000

Note: compared with before treatment, **P*<0.05.表 3 两组 T 淋巴细胞亚群水平比较($\bar{x} \pm s$)Table 3 Comparison of T lymphocyte subsets between the two groups($\bar{x} \pm s$)

Groups	CD4 ⁺ (%)		CD8 ⁺ (%)		CD4 ⁺ /CD8 ⁺	
	Before treatment	18 months after treatment	Before treatment	18 months after treatment	Before treatment	18 months after treatment
Control group (n=55)	38.06 $\pm$ 4.26	44.98 $\pm$ 5.36*	36.41 $\pm$ 3.05	31.87 $\pm$ 3.79*	1.05 $\pm$ 0.19	1.41 $\pm$ 0.24*
Study group(n=55)	38.23 $\pm$ 5.18	49.31 $\pm$ 4.57*	36.39 $\pm$ 4.91	27.23 $\pm$ 4.28*	1.05 $\pm$ 0.14	1.81 $\pm$ 0.26*
<i>t</i>	0.188	4.559	0.027	6.019	0.000	8.384
<i>P</i>	0.851	0.000	0.979	0.000	1.000	0.000

Note: compared with before treatment, **P*<0.05.

表 4 两组不良反应发生率比较【例(%)】

Table 4 Comparison of adverse reactions between the two groups[n(%)]

Groups	Nausea and vomiting	Slight liver function damage	Gastrointestinal discomfort	Dermatitis	Total incidence rate
Control group(n=55)	2(3.64)	2(3.64)	4(7.27)	1(1.82)	9(16.36)
Study group(n=55)	3(5.45)	3(5.45)	5(9.09)	2(3.64)	13(23.64)
χ^2					0.909
<i>P</i>					0.340

程较长,多伴有纤维空洞,这为结核菌的繁殖和生长提供了很好的条件,导致患者痰菌转阴极为困难,久治不愈^[15,16]。耐多药肺结核的发病机制复杂,不少研究显示耐多药肺结核的发生与结核分枝杆菌感染肺部后诱导系列细胞因子大量生成有

关^[17,18]。此外,机体免疫功能低下与肺结核的发病联系紧密。既往就有研究证实^[19],耐多药肺结核患者多伴免疫功能紊乱。利福霉素类药物是由地中海链丝菌产生的一类广谱抗生素,以利福布汀胶囊较为常见,该类药物亲脂性高,膜穿透能力极强,具

有较好的杀菌活性^[20-22]。由于左氧氟沙星的广泛应用甚至过度使用,致使左氧氟沙星的药效逐年下降^[23]。莫西沙星具有对常见耐药菌有效、不易产生耐药、抗菌谱广、半衰期长等优点^[24]。

本次研究结果显示, 研究组治疗 12 个月后、18 个月后疗效均高于对照组,可见利福布汀胶囊联合莫西沙星治疗耐多药肺结核,可有效阻止疾病进展。利福布汀胶囊的主要作用机制为通过结合 RNA 多聚酶 B 亚基抑制该酶的活性,直接抑制细菌细胞的合成,从而发挥抗菌效果^[25]。莫西沙星的作用机制主要是通过抑制细菌 DNA 旋转酶 A 亚单位活性达到阻断细菌 DNA 合成效果,与左氧氟沙星比较,其抗菌效果强且不会产生交叉耐药^[26]。两种药物从不同的作用机制出发,发挥协同抗菌作用。本次研究结果还显示,两组患者炎症因子和 T 细胞亚群均有所改善,且利福布汀胶囊联合莫西沙星治疗的改善效果更佳。TNF- α 具有多种生物活性,过量的 TNF- α 可导致组织干酪样变化甚至坏死;IL-6 可参与机体的炎症反应与病理生理过程,加剧机体的恶病质;CRP 是一种急性时相反应蛋白,当机体遇到任何病菌及感染源时其水平可急剧上升^[27]。CD8⁺ 可导致细胞功能产生紊乱,CD4⁺ 可发挥辅助调节作用。机体 CD4⁺/CD8⁺ 比值相对平衡、稳定,才可维持正常的免疫功能。既往研究结果显示,莫西沙星生物利用度高达 91%,渗透性极强。此外,该药在肺组织中药物浓度较高,利于药物发挥作用,可更加有效地调节患者的细胞因子及 T 细胞免疫水平。另研究组显示利福布汀胶囊联合莫西沙星治疗安全性较好。

综上所述, 利福布汀胶囊联合莫西沙星治疗耐多药肺结核,疗效显著,可有效改善炎症因子和 T 细胞亚群,且安全性较好,临床应用价值较高。

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