

doi: 10.13241/j.cnki.pmb.2020.06.019

莫西沙星联合用药方案对耐多药肺结核患者血清游离氨基酸和免疫功能的影响 *

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摘要 目的:探讨莫西沙星联合用药方案对耐多药肺结核(MDR-TB)患者血清游离氨基酸和免疫功能的影响。**方法:**选取 2015 年 9 月到 2018 年 1 月期间我院收治的 90 例 MDR-TB 患者,根据乱数表法将患者分为研究组(n=45)、对照组(n=45),其中对照组给予左氧氟沙星联合常规化疗治疗,研究组则给予莫西沙星联合常规化疗治疗,比较两组临床疗效、痰菌转阴率、病灶吸收率、空洞闭合率、血清游离氨基酸和免疫功能,记录两组治疗期间不良反应情况。**结果:**研究组治疗 18 个月后的临床总有效率为 71.11%(32/45),高于对照组的 46.67%(21/45)($P<0.05$)。研究组治疗 18 个月后痰菌转阴率、病灶吸收率、空洞闭合率均较对照组高($P<0.05$)。两组患者治疗 18 个月后 $CD4^+$ 、免疫球蛋白 A(IgA)、免疫球蛋白 G(IgG)均升高, $CD8^+$ 降低($P<0.05$),研究组治疗 18 个月后 $CD4^+$ 、IgA、IgG 高于对照组,而 $CD8^+$ 低于对照组($P<0.05$)。两组治疗 18 个月后缬氨酸、谷氨酸均升高,且研究组高于对照组($P<0.05$)。两组患者总不良反应发生率比较无明显差异($P>0.05$)。**结论:**莫西沙星联合常规化疗治疗 MDR-TB 的疗效确切,可有效改善患者血清游离氨基酸水平,提高机体免疫功能,同时不增加不良反应发生率。

关键词:莫西沙星;化疗;游离氨基酸;耐多药肺结核;免疫功能

中图分类号:R521 **文献标识码:**A **文章编号:**1673-6273(2020)06-1087-04

Effect of Moxifloxacin Combination Regimen on Serum Free Amino Acid and Immune Function in Patients with Multidrug-resistant Tuberculosis*

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ABSTRACT Objective: To investigate the effect of moxifloxacin combination regimen on serum free amino acid and immune function in patients with multidrug-resistant tuberculosis (MDR-TB). **Methods:** 90 patients with MDR-TB who were admitted to our hospital from September 2015 to January 2018 were selected, and they were divided into study group (n=45) and control group (n=45) according to random number table method. The control group was given levofloxacin combined with conventional chemotherapy, while the study group was given moxifloxacin combined with conventional chemotherapy. The clinical efficacy, sputum negative conversion rate, lesion absorption rate, cavity closure rate, serum free amino acid and immune function between two groups were compared. Adverse reactions during treatment were recorded. **Results:** The total effective rate of the study group at 18 months after treatment was 71.11%(32/45), which was higher than 46.67%(21/45) of the control group ($P<0.05$). 18 months after treatment, sputum negative conversion rate, lesion absorption rate and cavity closure rate of the study group were higher than those of the control group ($P<0.05$). 18 months after treatment, the $CD4^+$, immunoglobulin A (IgA) and immunoglobulin G (IgG) increased, and $CD8^+$ decreased of both groups ($P<0.05$). 18 months after treatment, the $CD4^+$, IgA and IgG of the study group were higher than those of the control group, while $CD8^+$ was lower than those of the control group ($P<0.05$). 18 months after treatment, the valine and glutamic acid increased of both groups, and those of the study group were higher than of the control group ($P<0.05$). There was no significant difference in the incidence of total adverse reactions of both groups ($P>0.05$). **Conclusion:** Moxifloxacin combined with conventional chemotherapy has a definite effect on MDR-TB, which can effectively improve the serum free amino acid level of patients, improve the immune function of the body, and it do not increase the incidence of adverse reactions.

Key words: Moxifloxacin; Chemotherapy; Free amino acid; Multidrug-resistant tuberculosis; Immune function

Chinese Library Classification(CLC): R521 **Document code:** A

Article ID: 1673-6273(2020)06-1087-04

* 基金项目:江苏省临床医学科技专项基金项目(20160479)

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(收稿日期:2019-10-06 接受日期:2019-10-28)

前言

结核病是指由结核分枝杆菌感染所引发的一种慢性传染性疾病,可侵袭多个脏器,其中以肺结核最为常见^[1]。耐多药肺结核(Multidrug-resistant tuberculosis, MDR-TB)则是指肺结核患者感染的结核杆菌通过体外被证实至少对异烟肼、利福平两种杀菌性抗结核药耐药^[2]。随着抗菌药物的广泛应用,加之部分初治患者不规范用药,导致MDR-TB的发病率呈逐年递增趋势,由于耐药的存在导致病情迁延不愈,已成为临床结核病的治疗难点^[3]。近年来的研究表明^[4],氟喹诺酮类抗菌药物治疗MDR-TB临床疗效较好。左氧氟沙星为氟喹诺酮类抗菌的代表药物,已被世界卫生组织指定为治疗MDR-TB的基本药物^[5]。莫西沙星抗菌谱广,为新一代氟喹诺酮类抗菌药物,因其渗透性强、吸收好、不良反应少而逐渐应用于临床^[6]。本研究通过对我院收治的45例MDR-TB患者给予莫西沙星联合用药方案治疗,疗效确切,现整理报道如下。

1 资料与方法

1.1 基线资料

选取我院收治的90例MDR-TB患者,选取时间为2015年9月到2018年1月。本研究通过了我院伦理委员会批准。纳入标准:(1)诊断标准参考《肺结核诊断和治疗指南》^[7];(2)经胸部CT检查确定患者肺部存在结核病变;(3)痰结核菌培养阳性;(4)体外被证实至少对异烟肼、利福平两种杀菌性抗结核药耐药;(5)知情本研究且签署了同意书;(6)年龄19-70岁,病程 ≤ 3 年。排除标准:(1)合并严重肝肾功能障碍者;(2)伴有急性慢性感染者;(3)合并其他部位结核者;(4)合并自身免疫、恶性肿瘤者;(5)合并高血压、糖尿病、高血脂等基础疾病者。根据乱数表法将患者分为研究组($n=45$)、对照组($n=45$),其中男36例,女9例,年龄21~70岁,平均 (42.73 ± 4.98) 岁;病程1~3年,平均 (2.09 ± 0.21) 年;病变肺叶:左肺16例,右肺14例,双肺15例;病变位置:上叶19例,下叶背段13例,上叶以及下叶背段13例。研究组男38例,女7例,年龄19~68岁,平均 (42.78 ± 5.82) 岁;病程1~2年,平均 (2.09 ± 0.37) 年;病变肺叶:左肺18例,右肺13例,双肺14例;病变位置:上叶18例,下叶背段14例,上叶以及下叶背段13例。两组一般资料比较无差异($P>0.05$)。

1.2 方法

对照组患者给予左氧氟沙星联合常规化疗方案,具体如下:硫酸阿米卡星注射液(华润双鹤利民药业有限公司,国药准字H37021164,规格:按 $C_{22}H_{43}N_5O_{13}$ 计算2 mL:0.2 g(20万单位)),静脉滴注,0.4 g/次,1次/d;利福喷丁胶囊(无锡福祈制药有限公司,国药准字H10940012,规格:0.15 g),口服,0.6 g/次,2次/周;帕司烟肼片(重庆华邦制药有限公司,国药准字H50022019,规格:0.1 g),口服,0.3 g/次,3次/d;盐酸乙胺丁醇片(瑞阳制药(上海)有限公司,国药准字H31020654,规格:0.25 g),口服,0.75 g/次,1次/d;乳酸左氧氟沙星片(浙江医药股份有限公司新昌制药厂,国药准字H20033922,规格:按 $C_{18}H_{20}FN_3O_4$ 计算0.2 g),口服,0.6 g/次,1次/d;吡嗪酰胺(沈阳红旗制药有限公司,国药准字H21022352,规格:0.25 g),口服,0.5 g/次,3次/d强化期采用阿米卡星、帕司烟肼片、利福喷丁、乙胺丁醇、

左氧氟沙星、吡嗪酰胺化疗6个月;巩固期采用利福喷丁、乙胺丁醇、帕司烟肼片、左氧氟沙星、吡嗪酰胺化疗18个月,总疗程18个月。研究组患者给予莫西沙星联合常规化疗方案,将对照组中的左氧氟沙星替换为莫西沙星(拜耳医药保健有限公司,国药准字J20150015,规格:0.4 g),口服,0.4 g/次,1次/d;其他治疗同对照组。两组患者在化疗过程中均采用水飞蓟宾葡甲胺片(江苏中兴药业有限公司,国药准字H32026233,规格:0.1 g)行保肝治疗,0.1 g/次,3次/d,并辅以营养支持治疗。

1.3 观察指标

(1)观察两组治疗18个月后的临床疗效^[8]。无效:胸部CT检查结果显示病情进展,临床症状恶化,痰结核菌培养为阳性。有效:胸部CT检查结果显示病变吸收或无明显变化,降低痰结核菌指数,空洞缩小,临床症状有所好转。显效:胸部CT检查结果显示病变吸收明显,空洞闭合或闭合 $\geq 50\%$,临床症状消失,痰结核菌培养为阴性。总有效率=显效率+有效率。(2)统计两组治疗9个月后、治疗18个月后的病灶吸收率、痰菌转阴率、空洞闭合率。其中病灶吸收根据胸部CT观察空洞缩小情况判定:恶化:治疗后病灶面积增加;不变:治疗后病灶面积无明显改变;吸收:治疗后病灶面积缩小 $<50\%$;显著吸收:治疗后病灶面积缩小 $>50\%$ 。病灶吸收率=显著吸收率+吸收率。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。空洞闭合根据胸部CT观察空洞缩小情况判定:增加:治疗后空洞直径增大;不变:治疗后空洞直径缩小 $<50\%$;缩小:治疗后空洞直径缩小 $>50\%$;闭合:治疗后空洞闭合。闭合率+缩小率=空洞闭合率。(3)记录两组治疗期间不良反应情况。(4)于治疗前、治疗18个月后抽取两组患者外周静脉血4 mL,以13 cm的离心半径,经4200 r/min离心15 min,分离待测。采用FACSCalibur流式细胞仪(美国BD公司生产)检测外周血T细胞亚群水平:CD4⁺、CD8⁺。采用酶联免疫吸附试验检测免疫球蛋白A(Immunoglobulin A, IgA)、免疫球蛋白G(Immunoglobulin G, IgG)水平以及血清游离氨基酸:缬氨酸、谷氨酸、甘氨酸、丝氨酸。

1.4 统计学方法

采用SPSS25.0软件分析数据。以率表示计数资料,行卡方检验。计量资料以均值 $\pm$ 标准差表示,组间比较行成组t检验,组内前后比较行配对t检验。 $\alpha=0.05$ 为检验标准。

2 结果

2.1 两组临床疗效比较

研究组治疗18个月后的临床总有效率为71.11%(32/45),高于对照组的46.67%(21/45)($P<0.05$);详见表1。

2.2 两组痰菌转阴率、病灶吸收率、空洞闭合率比较

两组治疗9个月后痰菌转阴率、病灶吸收率、空洞闭合率比较无明显差异($P>0.05$),治疗18个月后研究组病灶吸收率、痰菌转阴率、空洞闭合率均较对照组高($P<0.05$),详见表2。

2.3 两组免疫功能指标比较

两组患者治疗前CD4⁺、CD8⁺、IgA、IgG比较无明显差异($P>0.05$),两组患者治疗18个月后CD4⁺、IgA、IgG均升高,CD8⁺降低($P<0.05$),研究组治疗18个月后CD4⁺、IgA、IgG高于对照组,而CD8⁺低于对照组($P<0.05$),详见表3。

2.4 两组血清游离氨基酸比较

表 1 两组临床疗效比较 [例(%)]

Table 1 Comparison of clinical efficacy between two groups [n(%)]

Groups	Markedly effective	Effective	Invalid	Total effective rate
Control group(n=45)	7(15.56)	14(31.11)	24(53.33)	21(46.67)
Study group(n=45)	10(22.22)	22(48.89)	13(28.89)	32(71.11)
χ^2				5.553
P				0.018

表 2 两组痰菌转阴率、病灶吸收率、空洞闭合率比较 [例(%)]

Table 2 Comparison of sputum negative conversion rate, lesion absorption rate and cavity closure rate between two groups [n(%)]

Groups	Sputum negative conversion rate		Lesion absorption rate		Cavity closure rate	
	9 months after treatment	18 months after treatment	9 months after treatment	18 months after treatment	9 months after treatment	18 months after treatment
Control group(n=45)	5(11.11)	9(20.00)	4(8.89)	8(17.78)	5(11.11)	9(20.00)
Study group(n=45)	8(17.78)	18(40.00)	9(20.00)	19(42.22)	10(22.22)	21(46.67)
χ^2	0.809	4.286	2.248	6.402	2.000	7.200
P	0.368	0.038	0.134	0.011	0.157	0.007

表 3 两组免疫功能指标比较($\bar{x} \pm s$)Table 3 Comparison of immune function indexes between two groups($\bar{x} \pm s$)

Groups	CD4 ⁺ (%)		CD8 ⁺ (%)		IgA(g/L)		IgG(g/L)	
	Before treatment	18 months after treatment	Before treatment	18 months after treatment	Before treatment	18 months after treatment	Before treatment	18 months after treatment
Control group(n=45)	32.39± 7.23	36.24± 8.42*	37.98± 6.78	33.34± 6.54*	2.98± 0.85	3.54± 0.62*	10.36± 2.26	15.52± 3.42*
Study group(n=45)	32.41± 8.18	41.53± 7.33*	38.24± 7.65	29.38± 5.23*	3.05± 0.73	4.06± 0.61*	10.44± 2.87	19.83± 3.31*
t	0.012	3.179	0.171	3.172	0.419	4.011	0.147	6.075
P	0.990	0.002	0.865	0.002	0.676	0.000	0.884	0.000

Note: Compared with before treatment, * $P<0.05$.

两组治疗前缬氨酸、谷氨酸、甘氨酸、丝氨酸比较无明显差异($P>0.05$),详见表 4。丝氨酸比较无明显差异($P>0.05$),详见表 4。研究组高于对照组($P<0.05$),两组治疗前、治疗 18 个月甘氨酸、

2.5 不良反应发生情况比较

表 4 两组血清游离氨基酸比较($\bar{x} \pm s, \mu\text{mol/L}$)Table 4 Comparison of serum free amino acid between two groups($\bar{x} \pm s, \mu\text{mol/L}$)

Groups	Valine		Glutamate		Glycine		Serine	
	Before treatment	18 months after treatment	Before treatment	18 months after treatment	Before treatment	18 months after treatment	Before treatment	18 months after treatment
Control group(n=45)	236.49± 31.46	273.27± 29.38*	116.73± 23.44	132.12± 18.54*	302.27± 26.52	303.32± 20.17	173.62± 25.47	173.73± 19.32
Study group(n=45)	237.06± 32.65	309.15± 34.85*	117.73± 19.78	156.97± 24.68*	301.36± 25.79	302.91± 21.14	172.83± 22.43	173.21± 21.58
t	0.084	5.280	0.219	5.400	0.165	0.094	0.156	0.120
P	0.933	0.000	0.827	0.000	0.869	0.925	0.876	0.904

Note: Compared with before treatment, * $P<0.05$.

对照组治疗期间出现恶心呕吐 1 例、肠胃不适 4 例、轻微肝功能损伤 2 例、皮炎 1 例,不良反应发生率为 17.78%(8/45); 研究组治疗期间出现恶心呕吐 1 例、肠胃不适 1 例、轻微肝功能损伤 2 例、皮炎 1 例,不良反应发生率为 11.11%(5/45)。两组

患者总不良反应发生率比较无明显差异($\chi^2=0.809, P=0.368$)。

3 讨论

肺结核是临床常见的感染性疾病之一,主要由结核分枝杆菌感染引起,临床表现为全身中毒症状,如低热、乏力、盗汗等,是严重威胁人类健康及生活质量的疾病之一^[9,10]。近年来由于抗结核药物的滥用以及全球结核疫情的回升,致使结核分枝杆菌转变为耐药菌,MDR-TB 的出现已经无可避免^[11,12]。由于 MDR-TB 患者是同时耐最少两种有效的抗结核药药物,该病不仅治疗较为困难,同时还有可能因不可治愈而持续传播耐多药结核菌,提高原发性 MDR-TB 的发病风险^[13-15]。既往相关调查显示^[16],我国的肺结核涂阳患者耐多药率为 8.32%,且 MDR-TB 的发病率在全球范围内呈现增长趋势,给肺结核的防治工作带来极大的挑战。常规化疗用药方案是临床治疗 MDR-TB 的常用措施,尽管不少临床实践已遵循世界卫生组织制定的 MDR-TB 治疗原则,但常规化疗用药方案的有效率始终徘徊在 30%~40%,且不少 MDR-TB 患者可逐渐成为慢性传染源^[17,18]。因此,寻找新的有效的治疗方式对于改善 MDR-TB 患者预后具有积极的临床意义。莫西沙星和左氧氟沙星均属于氟喹诺酮类药物^[19,20],两者均具有杀死细胞内外耐药结核杆菌的作用,现临床对于上述两种药物的疗效尚存在一定争议,本研究就此展开探讨。

本次研究结果中研究组治疗后的痰菌转阴率、临床总有效率、病灶吸收率、空洞闭合率均较对照组优,可见莫西沙星联合常规化疗治疗 MDR-TB,可进一步优化治疗效果。分析其原因,左氧氟沙星使 DNA 旋转酶受到抑制而发挥抗结核杆菌活性作用^[21]。而莫西沙星双环 8- 位上的甲氧基能够优化分子结构,可使其对细胞膜穿透破坏力及对细菌亲和力增加,组织内血药浓度高,渗透性强,口服后的生物利用度可高达 90%,相较于左氧氟沙星而言,莫西沙星还具有更高的抗菌性^[22-24]。T 淋巴细胞亚群是反映患者细胞免疫功能最直接的指标,肺结核患者的 T 淋巴细胞亚群通常表现为 CD4⁺/CD8⁺ 降低,CD8⁺ 升高^[25]。IgA 及 IgG 是一种重要因子,可影响体液免疫功能,血清含量可有效反映体液免疫功能^[26]。同时体外实验证实^[27],缬氨酸、谷氨酸是结核菌主要的氮来源,而甘氨酸、丝氨酸则无法被结核菌利用。当患者处于肺结核时,结核菌大量繁殖,谷氨酸、缬氨酸内的氮分子将被利用,最终导致患者游离氨基酸低表达。本次研究结果中,两组患者血清游离氨基酸及免疫功能经治疗后均有所改善,且研究组的改善效果更佳。可见相比于左氧氟沙星,莫西沙星可获得更好的治疗效果。这可能是因为莫西沙星可有效抑制结核分枝杆菌的增殖,减少其对宿主的进一步损害,减少氮的利用率,进而有效改善患者血清游离氨基酸水平,提高机体免疫功能^[28-30]。由于恶心呕吐、肠胃不适、皮炎是抗结核药物引起的最常见的不良反应,同时 MDR-TB 治疗周期长,治疗药物多,患者易出现肝损害,本研究中两组患者总不良反应发生率比较无明显差别,可见莫西沙星联合常规化疗治疗,安全性较好。

综上所述,莫西沙星联合常规化疗治疗 MDR-TB,疗效确切,可有效改善患者血清游离氨基酸水平,提高机体免疫功能,同时不增加不良反应发生率,具有一定的临床应用价值。

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