doi: 10.13241/j.cnki.pmb.2018.21.026

利福喷丁对肺结核患者血清 IL-6、IFN-γ、CA125 水平的影响 *

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摘要 目的：探讨利福喷丁对肺结核患者的治疗效果及对血清白介素(IL)-6、干扰素(IFN)-γ、CA125 的影响。**方法：**选择 2013 年 1 月至 2016 年 4 月我院接诊的 96 例肺结核患者，通过随机数表法分为观察组(n=48)和对照组(n=48)。在常规抗结核方案基础上，对照组使用利福平，观察组使用利福喷丁。比较两组治疗前后用力肺活量(FVC)、第一秒用力呼气容积(FEV1)、最大通气量(MVV)、血清 IL-6、IFN-γ、CA125 水平、临床疗效及不良反应的发生情况。**结果：**治疗后，观察组用力肺活量(FVC)、第一秒用力呼气容积(FEV1)、最大通气量(MVV)、临床疗效总有效率均明显高于对照组(P＜0.05)；血清 IL-6、IFN-γ、CA125 水平、白细胞下降、肝功异常、皮疹、胃肠道反应发生率均显著低于对照组(P＜0.05)。**结论：**利福喷丁治疗肺结核的临床效果显著，可明显改善患者的肺功能，降低患者血清 IL-6、IFN-γ、CA125 的水平，且安全性高。

关键词：肺结核；利福喷丁；利福平；抗结核治疗

中图分类号：R521 **文献标识码：**A **文章编号：**1673-6273(2018)21-4118-04

Efficacy of Rifapentine in the Treatment of Tuberculosis and Its Effects on the Serum Levels of IL-6, IFN-γ and CA125*

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ABSTRACT Objective: To study the clinical efficacy of rifapentine and its effect on the serum levels of interleukin(IL)-6, interferon (IFN)-γ and CA125 of patients wuth tuberculosis. **Methods:** 96 patients with tuberculosis who were treated in our hospital from January 2013 to April 2016 were selected and randomly divided into the observation group (n=48) and the control group (n=48). On the basis of routine anti tuberculosis scheme, the patients in the control group were treated with rifampicin, while the patients in the observation group were treated with rifapentine. Then the serum levels of IL-6, IFN-γ and CA125, the respiratory function, the clinical curative effect and the adverse reactions in the two groups were observed and compared before and after the treatment. **Results:** After treatment, the forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and maximal ventilation volume (MVV) in the observation group were significantly higher than those of the control group (P<0.05). The serum levels of IL-6, IFN-γ and CA125 n the observation group were significantly lower than those of the control group (P<0.05). The total effective rate in the observation group was significantly higher than that of the control group (P<0.05). The incidence rate of leukopenia, abnormal liver function, rash and gastrointestinal reactions in the observation group was significantly lower than that of the control group (P<0.05). **Conclusion:** Rifapentine was effective for tuberculosis, which could effectively reduce the expression of serum IL-6, IFN-γ and CA125 and improve the lung function with high security.

Key words: Tuberculosis; Rifapentine; Rifampicin; Anti tuberculosis treatment

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

Article ID: 1673-6273(2018)21-4118-04

前言

肺结核主要是由结合分歧杆菌所引发的慢性传染性疾病，在人体免疫力较差时，结核病会侵袭到其余器官，最常见的则是肺部结核感染，主要临床症状表现为咳嗽、发热、咳痰、咳血、无力、胸痛等[1,2]。近年来，该病发病率不断攀升，已成为危害人体健康的重要疾病。目前，对于抗结核治疗的原则主要是联合规律性用药，其中首选方案则是利福霉类药物并加以其余抗结核药的联合，利福平、利福喷丁均属于福霉素类杀菌药物，但其疗效及安全性仍存在着较多争议[3,4]。为选择更安全有效的抗结核方案，本研究在常规抗结核治疗基础上，分别给予肺结核患者利福平、利福喷丁的治疗，并对比观察其疗效，现报道如下。

* 基金项目：湖北省自然科学基金项目(2010CDB09205)

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(收稿日期：2018-03-06 接受日期：2018-03-31)

1 资料与方法

1.1 临床资料

选择 2013 年 1 月至 2016 年 4 月我院接诊的 96 例肺结核患者。纳入标准[5]:① 符合肺结核诊断标准,并通过痰结核菌培养、X 线检查得以证实;② 年龄 18~60 岁;③ 同意此次研究。排除标准[6]:① 对此次药物不适用;② 伴有心、肝、肾等严重器质性疾病;③ 伴有血液系统、消化系统、神经系统、免疫性疾病;④ 中途中断研究;⑤ 依从性差。通过随机数表法分为两组,各 48 例。观察组男 24 例,女 24 例;年龄 19~57 岁,平均(38.47± 3.64)岁;病程 1~10 个月,平均(4.74± 0.91)月;初治 35 例,复治 13 例。对照组男 27 例,女 21 例;年龄 20~59 岁,平均(38.28± 3.87)岁;病程 1~9 个月,平均(4.79± 0.85)月;初治 37 例,复治 11 例。本次研究已获得我院伦理委员会批准实施,两组一般资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

两组均给于常规抗结核方案,0.75 g 乙酰丁醇 (规格 0.25 g,厂家:沈阳红旗制药有限公司,国药准字 H21022349),1.25 g 吡嗪酰胺(规格 0.25 g,厂家:广东台城制药股份有限公司,国药准字 H44020947),0.3 g 异烟肼(规格 0.1 g,厂家:广东华南药业集团有限公司,国药准字 H44020699),1 次 /d。对照组再使用利福平(规格 0.15 g,厂家:广东华南药业集团有限公司,国药准字 H44020771)治疗,剂量 0.45 g/ 次,1 次 /d。观察组使用利福喷丁(规格 0.15 g,厂家:上海信谊万象药业股份有限公司,国药准字 H10940199)治疗,剂量 0.6 g/ 次,2 次 / 周。均连续治疗 6 个月。

1.3 观察指标

① 用力肺活量(FVC)、第一秒用力呼气容积(FEV1)、最大通气量(MVV),仪器使用日本捷斯特 CHESTAC-8800 肺功能测定仪;② 抽取空腹静脉血 3 mL,使用酶联免疫吸附法测定白介素(IL)-6、干扰素(IFN)-γ 以及 CA125 水平,试剂盒均购于美国 RD 公司;③ 记录治疗过程中白细胞下降、肝功异常、皮疹、胃肠道反应的发生率。

1.4 疗效评定标准

显效:治疗后咳嗽、发热、胸痛、咳痰等临床症状消失或明显缓解,痰菌检查转阴,通过 X 线检查显示病灶吸收程度≥ 1/2;有效:治疗后临床症状有所缓解,痰菌检查阳性率有所降低,通过 X 线检查显示病灶吸收程度<1/2;无效:治疗后未达到上述标准,或加重。

1.5 统计学分析

采用 SPSS18.0 软件包处理,计量资料以均数± 标准差($\bar{x}$± s)表示,采用 t 检验,计数资料以例(%)表示,采用 χ^2 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效对比

观察组总有效率为 93.75%,显著高于对照组 68.75%(P<0.05),见表 1。

表 1 两组临床疗效对比(例,%)

Table 1 Comparison of the clinical efficacy between two groups (n, %)

Groups	Effective	Valid	Invalid	Total effective rate
Observation group(n=48)	26(54.17)	19(39.58)	3(6.25)	45(93.75)*
Control group(n=48)	15(31.25)	18(37.50)	15(31.25)	33(68.75)

Note: Compared with the control group, *P<0.05.

2.2 两组治疗前后呼吸功能对比

治疗前,两组 FVC、FEV1、MVV 比较差异无统计学意义(P>0.05);治疗后,两组 FVC、FEV1、MVV 较治疗前均显著改善(P<0.05),且观察组 FVC、FEV1、MVV 改善程度较对照组更明显(P<0.05),见表 2。

表 2 两组治疗前后呼吸功能对比($\bar{x}$± s,%)

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

Groups		FVC	FEV1	MVV
Observation group(n=48)	Before treatment	67.45± 3.40	65.42± 4.19	51.23± 3.17
	After treatment	85.62± 4.34*#	79.85± 5.62*#	65.50± 3.54*#
Control group(n=48)	Before treatment	67.59± 3.37	65.27± 4.35	51.29± 3.12
	After treatment	78.15± 4.02*	71.49± 4.74*	57.82± 3.27*

Note: Compared with the same group, *P<0.05; compared with the control group, #P<0.05.

2.3 两组治疗前后血清 IL-6、IFN-γ、CA125 水平对比

治疗前,两组血清 IL-6、IFN-γ、CA125 水平比较差异均无统计学意义(P>0.05);治疗后,两组血清 IL-6、IFN-γ、CA125 水平均较治疗前显著降低(P<0.05),且观察组血清 IL-6、IFN-γ、CA125 水平均明显低于对照组(P<0.05),见表 3。

2.4 两组不良反应发生情况的比较

观察组白细胞下降、肝功异常、皮疹、胃肠道反应的发生率均显著低于对照组(P<0.05),见表 4。

表 3 两组治疗前后血清 IL-6、IFN-γ、CA125 水平比较($\bar{x}\pm s$)

Table 3 Comparison of the serum IL-6, IFN-γ and CA125 levels between two groups ($\bar{x}\pm s$)

Groups		IL-6(pg/mL)	IFN-γ(pg/mL)	CA125(U/mL)
Observation group(n=48)	Before treatment	43.41± 6.73	116.05± 6.82	187.45± 14.03
	After treatment	11.94± 2.10*#	87.62± 4.15*#	78.94± 5.72*#
Control group(n=48)	Before treatment	43.54± 6.67	115.93± 6.96	188.12± 12.95
	After treatment	24.32± 4.52*	101.26± 5.33*	123.40± 8.51*

Note: Compared with the same group, *P＜0.05; compared with the control group, #P＜0.05.

表 4 两组不良反应发生情况的比较(例,%)

Table 4 Comparison of the incidence of adverse reactions between the two groups (n, %)

Groups	Leukopenia	Abnormal liver function	Rash	Gastrointestinal reaction
Observation group(n=48)	2(4.17)*	5(10.42)*	1(20.83)*	3(6.25)*
Control group(n=48)	9(18.75)	16(33.33)	7(14.58)	12(25.00)

Note: Compared with the control group, *P＜0.05.

3 讨论

利福霉类药物在抗结核治疗中起着重要作用,在口服利福平、利福喷丁后,其药物成分可迅速到达机体内并吸收,并在多种器官组织、循环系统中广泛分布,在肝脏内的药物浓度最高,可轻易进入肝脏细胞,也可在肺组织纤维性空洞、痰液中发挥作用[8,9]。但有较多药理研究显示无论是在血液浓度的半衰期还是高峰期中,利福喷丁的效果均优于利福平[10]。Lines G 等[11]证实利福喷丁的抗菌活性也优于利福平,其半衰期大约在 12 h,且用药后 7 h 则达到血药浓度最大值,兼有高效、长效的特效。且利福喷丁对结核杆菌具有抑制作用,其抑制浓度一般在 0.11~0.26 g/mL,而利福平的抑制浓度仅有 0.05~0.13 g/mL,只有利福喷丁的二分之一[12]。本研究结果显示利福喷丁的治疗效果明显比利福平更具有优势,应用利福喷丁的患者总有效率高达 93.75%,且呼吸功能明显提高。这与 Stennis NL 等[13]研究具有相似性。

结核病的发病过程较为复杂,与机体自身免疫力的强弱、免疫细胞分泌细胞因子之间的动态平衡之间存在着密切的关系[14]。IL-6 可诱导 B 细胞分化以及产生抗体,并可诱导 T 细胞的活化、增值、分化,在机体免疫应答中起着重要作用[15]。IFN-γ 在细胞免疫、体液免疫中均发挥着免疫调节的作用,而对巨噬细胞、NK 细胞可发挥一定的增强免疫作用。Ravimohan S 等[16]的研究显示 IL-6、IFN-γ 表达情况为健康人群＜结核分枝杆菌感染＜肺结核患者,其在肺结核的发病中起着重要作用。本研究结果显示利福喷丁治疗的患者血清 IL-6、IFN-γ 表达比利福平治疗的患者更低,与利福喷丁具有更强的抗菌活性有关,可能因其可有效杀灭结核杆菌,缓解机体炎症反应。

CA125 是一种高分子量糖蛋白,在较多肺恶性疾病如结核性胸膜炎、慢性非阻塞性肺疾病、肺结核中的表达上调。有研究显示在肺结核患者血清 CA125 水平较健康人群明显增加,主要是由于在肺结核患者中,支气管、肺组织出现受损,而当胸膜受到创伤、炎症等刺激时,则会释放高水平的 CA125[17]。Ma J 等[18]研究显示经过抗结核治疗后,随着肺部影像学、痰菌转阴的好转,血清 CA125 逐渐降低,且经过半年治疗后,其表达可恢复到正常水平。在本研究中,经过利福喷丁治疗的患者 CA125 表达更低,可能是由于治疗后,肺组织得到恢复,CA125 的释放减少。

在抗结核治疗中,肝功能损伤是最明显的并发症,症状轻微的患者只表现为部分肝脏功能损伤,若症状严重,甚至可能引发死亡,因此减少抗结核治疗过程中的不良反应十分重要[19]。本研究显示使用利福喷丁的患者肝功异常发生率明显比利福平患者更低,且白细胞下降、皮疹、胃肠道反应的发生率也较低,显示出利福喷丁治疗安全性更高,更适用于结核化疗中。此外,由于利福喷丁的蛋白结合率高达 95%,和疗效更持久之间存在着密切的关系,在组织停留时间更长,因此 2 次 / 周用药即可,间歇性用药方式更合适[20]。

综上所述,利福喷丁治疗肺结核的临床效果显著,可明显改善患者的肺功能,降低患者血清 IL-6、IFN-γ、CA125 的水平,且安全性高。

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