doi: 10.13241/j.cnki.pmb.2017.09.028

维生素 D 联合抗结核药物对老年脊柱结核患者血清 IL-1β 及干扰素γ 水平的影响 *

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摘要 目的：探究维生素 D 联合抗结核药物对老年脊柱结核患者血清白细胞介素 -1β（IL-1β）及干扰素γ（IFN-γ）水平的影响。**方法：**选取 2014 年 7 月到 2016 年 7 月我院诊治的老年脊柱结核患者 96 例为研究对象，随机分为对照组(48 例)与试验组(48 例)。对照组给予正规抗结核治疗，试验组在对照组基础上给予维生素 D 滴剂治疗。比较两组患者 VAS 评分、脊髓损伤程度、血清 IL-1β 及干扰素γ 水平。**结果：**治疗结束后，两组患者 VAS 评分均较治疗前降低(P<0.05)，脊髓损伤程度减轻(P<0.05)，血清 IL-1β 及 IFN-γ 水平均较治疗前降低(P<0.05)；与对照组相比，试验组 VAS 评分较对照组低(P<0.05)，脊髓损伤程度减轻更为显著(P<0.05)，试验组血清 IL-1β 及 IFN-γ 水平较对照组低(P<0.05)。**结论：**维生素 D 联合抗结核药物对老年脊柱结核患者的疗效显著，患者疼痛明显减轻，推测其与血清 IL-1β 及干扰素 γ 水平降低有关。

关键词：维生素 D；抗结核药物；老年脊柱结核；白细胞介素 -1β（IL-1β）；干扰素 γ（IFN-γ）

中图分类号：R529.2 **文献标识码：**A **文章编号：**1673-6273(2017)09-1707-03

Effect of Vitamin D Combined with Anti Tuberculosis Drugs on the Serum Levels of IL-1 and Interferon Gamma of Elderly Patients with Spinal Tuberculosis*

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ABSTRACT Objective: To investigate the effect of Vitamin D combined with anti tuberculosis drugs on the serum levels of IL-1 and interferon gamma of elderly patients with spinal tuberculosis. **Methods:** 96 elderly patients with spinal tuberculosis in our hospital from July 2014 to July 2016 were selected and randomly divided into the control group and the experiment group, with 48 cases in each group. The control group was treated by regular anti tuberculosis treatment and the experiment group was treated on the base of the control group with Vitamin D Drops. 8 weeks for a course of treatment, a total of a course of treatment. The VAS score, degree of spinal cord injury, serum levels of IL-1 and interferon gamma were compared between two groups after treatment. **Results:** Compared with before treatment, the VAS scores of two groups were lower after treatment (P<0.05), the degrees of spinal cord injury were less (P<0.05), the serum IL-1β and IFN-γ levels were lower (P<0.05). Compared with the control group, the VAS score was lower the in the experiment group (P<0.05), the degree of spinal cord injury was less (P<0.05), the serum IL-1β and IFN-γ levels were lower (P<0.05). **Conclusion:** Vitamin D combined with anti tuberculosis drugs could significantly reduce the pain and the degree of spinal cord injury in elderly patients with spinal tuberculosis, which might be related to the decrease of serum IL-1 beta and interferon gamma levels.

Key words: Vitamin D; Anti tuberculosis drugs; Senile spinal tuberculosis; IL-1β; IFN-γ

Chinese Library Classification(CLC): R529.2 Document code: A

Article ID: 1673-6273(2017)09-1707-03

前言

随着耐药结核、HIV 感染的不断增加，结核病的发病率也随之增加，其中脊柱结核占骨与关节结核 50%以上，临床表现为病损部位疼痛、肌肉痉挛等，严重者表现为脊柱塌陷、变形，一旦压迫脊髓、神经根，则会并发截瘫等，因此及时有效的治疗十分重要[1]。目前，单纯使用抗结核药物治疗效果有限，探索一种新型有效的药物具有重要的意义[2]。研究表明维生素 D 能够能够调节机体免疫系统，提高机体抗结核杆菌的能力，对于结核病有一定的治疗效果[3]。IL-1β 属于前炎症因子，主要由 MPS 产生，具有免疫调节功能。而干扰素γ 作为一种细胞因子，能够调节与免疫相关基因的转录，从而调节免疫反应，血清中的这两种指标水平均能够作为反映脊柱结核病情进展的指标[4,5]。本研究以老年脊柱结核患者为研究对象，探讨维生素 D 联合抗结

* 基金项目：四川省卫生厅科研项目（100153）

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(收稿日期：2016-09-28 接受日期：2016-10-23)

核药物对老年脊柱结核患者血清 IL-1β 及干扰素 γ 水平影响。

1 资料与方法

1.1 临床资料

收集 2014 年 7 月～2016 年 7 月我院诊治老年脊柱结核患者 96 例,其中颈椎 10 例,胸椎 42 例,腰椎 36 例,骶椎 8 例。按随机数字表法将 96 例入选者随机分配为试验组与对照组,试验组 48 例,男女比为 26/22,平均年龄(67.37± 8.68)岁,平均病程(2.13± 0.69)年;对照组 48 例,男女比为 27/21,平均年龄(68.19± 8.50)岁,平均病程(2.11± 0.79)年。两组入选者一般资料无统计学差异(P>0.05),具有可比性。本试验经伦理委员会审核,准许在我院开展,同时入选者知情本试验具体方案,并同意参与。

纳入患者临床表现、影像学检查及实验室检查诊断为脊柱结核;患者年龄 60~80 岁;患者签署知情同意书。排除 HIV 感染者;脊柱结核合并完全性截瘫者;合并有其他部位活动性结核患者;用药期间行手术治疗者;恶性肿瘤患者;合并严重心、肝、肺等脏器功能障碍患者;自身免疫性疾病患者;患者存在精神障碍,无法配合。

1.2 治疗方法

对照组给予正规抗结核治疗,应用 4 联抗结核药物,异烟肼片(成都锦华药业有限公司,国药准字 H51020789),每日 5 mg/kg,利福平片(成都锦华药业有限公司,国药准字 H51020873),每日 0.5 g,乙胺丁醇(广东华南药业集团有限公司,国药准字 H44020758),每日 15 mg/kg,硫酸链霉素片(江苏神华药业有限公司,国药准字 H32024528),肌肉注射 1 g,每周给药 2 次。试验组在对照组的基础上联合给予口服维生素 D 滴剂(青岛双鲸药业有限公司,国药准字 H20113033),每日 2 粒。8 周为一个疗程,共治疗一个疗程。

1.3 观察指标

1.3.1 视觉模拟疼痛评分 采用视觉模拟疼痛评分(VAS)对治疗前后患者脊柱结核疼痛程度进行评估,使用一条 10 cm 的游动标尺,0 代表 " 无痛 ",10 代表 " 疼痛剧烈 ",记录疼痛评分。

1.3.2 脊髓损伤分级 采用 Frankel 脊髓损伤分级方法对治疗前后患者脊髓损伤进行评估,共分为 A、B、C、D 及 E 五个等级。A:损伤平面以下深浅感觉完全消失;B:损伤平面以下深浅感觉完全消失,仅存某些骶区感觉;C:损伤平面以下仅有某些肌肉运动功能,无有用功能存在;D:损伤平面以下肌肉功能不完全,可扶拐行走;E:深浅感觉、肌肉功能及大小便功能良好,可有病理反射。

1.3.3 血清 IL-1β 及 IFN-γ 水平 所有患者在接受治疗前及治疗完成后,采集患者空腹静脉血 10 mL,静置 30 分钟后,3000 rpm 离心 15 分钟,将血清分离,-80℃保存。待所有样品收集完毕后,统一检测。采用酶联免疫吸附(ELISA)技术,使用由北京博奥龙免疫技术有限公司提供的 ELISA 试剂盒检测血清 IL-1β 及 IFN-γ 水平。主要步骤:① 将包被抗体的酶标板平衡室温,加入样品每孔 100 μL,37℃孵育 2 h,洗涤液清洗 5 次;② 加入 HRP 标记的二抗 100 μL,37℃孵育 1 h,洗涤液清洗 5 次;③ 加入 TMB 100 μL 显色,室温反应 15 分钟,使用酶标仪读取 OD 值,绘制标准曲线,记录样本浓度。上述操作均有专业人员统一完成。

1.4 统计学指标

数据处理使用 SPSS17.0 进行统计学分析,血清 IL-1β 及 IFN-γ 水平、VAS 评分采用均数± 标准差表示,使用 t 检验分析有无统计学差异,脊髓损伤分级使用秩和检验统计分析,均以 P<0.05 具有统计学差异。

2 结果

2.1 两组治疗前后 VAS 评分的比较

治疗前,两组患者疼痛程度无明显差异(P>0.05)。治疗后,两组患者的 VAS 评分均较治疗前显著降低(P<0.05),且试验组 VAS 评分较对照组低(P<0.05)。见表 1。

表 1 两组患者治疗前后 VAS 评分的比较($\bar{x}$± s)

Table 1 Comparison of the VAS score between two groups before and after treatment($\bar{x}$± s)

Groups	Time	VAS score
Control group	Before treatment	8.12± 1.15
(n=48)	After treatment	6.27± 0.82*
Experiment group	Before treatment	8.27± 1.08
(n=48)	After treatment	4.10± 0.73*#

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

2.2 两组治疗前后脊髓损伤分级的比较

治疗结束后,两组患者脊髓损伤均有所减轻(P<0.05),与对照组相比,试验组脊髓损伤减轻更为显著(P<0.05),见表 2。

表 2 两组患者治疗前后脊髓损伤分级比较(例)

Table 2 Comparison of the grading of spinal cord injury between two groups before and after treatment (n)

Groups	Time	A	B	C	D	E
Control group	Before treatment	0	0	5	28	15
(n=48)	After treatment	0	0	1	21	26
Experiment group	Before treatment	0	0	4	28	16
(n=48)	After treatment	0	0	0	17	31

Note: Compared with before treatment, P<0.05.

2.3 两组治疗前后血清 IL-1β 及 IFN-γ 水平比较

治疗前,两组患者血清 IL-1β 及 IFN-γ 水平无明显差异(P>0.05)。治疗后,对照组单纯应用抗结核药物组及试验组维生素 D 联合抗结核药物组血清 IL-1β 及 IFN-γ 水平均较治疗前

降低(P<0.05);与对照组相比,试验组维生素 D 联合抗结核药物组血清 IL-1β 及 IFN-γ 水平较对照组单纯应用抗结核药物组低(P<0.05),见表 3。

表 3 两组患者治疗前后血清 IL-1β 及 IFN-γ 水平比较($\bar{x}\pm s$)

Table 3 Comparison of the serum IL-1β and IFN-γ levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	Time	IL-1β(pg/mL)	IFN-γ(pg/ml)
Control group	Before treatment	10.09± 2.36	51.78± 11.68
(n=48)	After treatment	8.22± 1.07*	44.17± 9.81*
Experiment group	Before treatment	10.23± 2.41	53.52± 12.34
(n=48)	After treatment	4.87± 0.86*#	35.16± 7.53*#

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

3 讨论

目前,大多数结核病患者联合应用多种抗结核药物,包括异烟肼、利福平、乙胺丁醇及链霉素等,但是单纯使用抗结核药物治疗效果有限,探索一种新型有效的药物具有重要的意义[6,7]。研究显示血清维生素 D 缺乏是结核病发生的独立危险因子[8-11]。而维生素 D 不仅能够调节钙盐代谢,调节骨稳态,同时能够能够调节机体免疫系统,激活细胞免疫及单核细胞抑制结合杆菌生长,从而提高机体抗结核杆菌的能力,对于结核病有一定的治疗效果[11-13]。本研究以 96 例老年脊柱结核患者为研究对象,探讨维生素 D 联合抗结核药物对老年脊柱结核患者临床疗效。结果显示:与单纯使用抗结核药物相比,维生素 D 联合抗结核药物治疗患者的 VAS 评分明显降低,脊髓损伤程度减轻,说明维生素 D 联合抗结核药物能够有效抑制结合抗菌生长,治疗脊柱结核,患者疼痛明显减轻,脊髓损伤程度减轻。

IL-1β 属于前炎症因子,主要由 MPS 产生,能够激活其他细胞因子,从而激活 T 淋巴细胞,同时还能够促进 B 淋巴细胞增殖、分化,促进免疫球蛋白的产生[14]。当结核杆菌感染时,体内 IL-1β 分泌增加,发生一系列免疫反应,从而导致机体损伤[15-17]。而干扰素γ作为一种细胞因子能够调节与免疫相关基因的转录,从而调节免疫反应[18],当结合杆菌感染时,免疫系统被激活,由于反复受到结核杆菌抗原的刺激,体内 IFN-γ 产生增加[19,20]。因此,血清中的这两种指标均能够作为反映脊柱结核病情进展的指标[15]。本研究中,治疗结束后,两组患者血清 IL-1β 及 IFN-γ 水平均较治疗前降低,与对照组相比,试验组维生素 D 联合抗结核药物治疗血清 IL-1β 及 IFN-γ 水平较对照组低,推测维生素 D 联合抗结核药物治疗脊柱结核的分子生物学机制为调节血清 IL-1β 及 IFN-γ 水平,从而调节免疫反应,减轻患者临床症状。

综上所述,维生素 D 联合抗结核药物对老年脊柱结核患者疗效显著,患者疼痛及脊髓损伤程度减轻,推测可能与血清白介素 1β 及干扰素γ水平降低有关。

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急性生理学及慢性健康状况评分 II(APACHEII) 是国内外广泛应用的一个危重病评分系统,能够较为准确评价危重患者病情严重程度和预后 [19]。本研究结果显示，最终得出回归方程：Logit P=0.00017*PCT+0.0297* 胆源性结石病史 +0.093*APACHEII 评分 -0.193;最终方程解释为 PCT(第 7d)水平越高，具有胆源性结石病史、APACHEII 评分(第 1d)评分越高,发生重症胰腺炎的概率越大,往往提示预后较差。

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