临床与基础桥接研究
Clinical and Basic Bridging Research

阴道用乳杆菌活菌胶囊治疗复发性外阴阴道念珠菌病患者的临床研究

Clinical trial of vaginal live *Lactobacillus* capsule in the treatment of patients with recurrent vulvovaginal candidiasis

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摘要:目的 观察阴道用乳杆菌活菌胶囊联合硝呋太尔制霉素阴道软胶囊用于复发性外阴阴道念珠菌病(RVVC)患者的临床效果及对患者阴道微生态环境的影响。**方法** 将RVVC患者按照队列法分为对照组及试验组,对照组患者给予硝呋太尔制霉素阴道软胶囊,睡前1粒阴道栓塞治疗,试验组患者予以阴道用乳杆菌活菌胶囊0.25 g,晨起阴道局部用药联合硝呋太尔制霉素阴道软胶囊睡前1粒阴道栓塞治疗,2组初始治疗时间均持续7 d,停药7 d后均进行阴道分泌物病原菌培养,阴性者为治愈。治愈者进行硝呋太尔制霉素阴道软胶囊巩固治疗,每周1次,持续6个月。比较2组患者的临床治疗效果,比较2组患者治疗前及治疗7 d后阴道微生态及阴道分泌物人β防御素(HβD)-3、白细胞介素(IL)-1β、IL-8变化情况,并进行安全性评价。**结果** 本研究共入组268例,其中试验组136例,对照组132例。试验组和对照组初始治疗真菌学治愈率分别为84.56%(115例/136例)和73.48%(97例/132例),巩固治疗真菌学治愈率分别为82.61%(95例/115例)和70.10%(68例/97例),在统计学上差异均有统计学意义(均$P<0.05$)。治疗7 d后,试验组及对照组的阴道清洁度Ⅲ~Ⅳ级占比分别为24.26%和36.36%,阴道菌群密集度Ⅱ~Ⅲ级占比分别为79.41%和68.18%,阴道菌群多样性Ⅱ~Ⅲ级占比分别为77.94%和65.91%,优势菌为乳杆菌的占比分别为82.35%和68.18%,阴道分泌物HβD-3水平分别为(129.65±11.51)和(135.87±10.46)pg·mL^{-1},IL-1β水平分别为(65.48±9.27)和(72.46±10.38)pg·mL^{-1},IL-8水平分别为(159.36±12.50)和(176.30±13.19)pg·mL^{-1},在统计学上差异均有统计学意义(均$P<0.05$)。试验组和对照组患者的药物不良反应总发生率分别为23.53%(32例/136例)和18.38%(25例/132例),在统计学上差异无统计学意义($P>0.05$)。**结论** 阴道用乳杆菌活菌胶囊联合硝呋太尔制霉素阴道软胶囊治疗相较于硝呋太尔制霉素软胶囊单独治疗,可以改善RVVC患者阴道微生态,治疗阴道用阴道真菌感染治愈率更高,具有较好的安全性。

关键词:乳杆菌活菌胶囊;硝呋太尔制霉素阴道软胶囊;复发性外阴阴道念珠菌病;阴道微生态;强化;巩固
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Abstract: Objective To observe the clinical effect of live vaginal *Lactobacillus* capsule for vaginal use combined with nifuratel nystatin vaginal soft capsule on patients with recurrent vulvovaginal candidiasis (RVVC) and its influence on vaginal microecological environment of patients. **Methods** The RVVC patients were divided into the control group and the treatment group according to the cohort method. The

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patients in the control group were treated with one grain of vaginal embolization before going to bed with nifuratel nystatin vaginal soft capsule. The patients in the treatment group were treated with 0.25 g of vaginal live *Lactobacillus* capsule in the morning combined with one grain of vaginal embolization before going to bed with nifuratel nystatin vaginal soft capsule. The initial treatment time of the two groups lasted for 7 days. Initial treatment lasted for 7 days in both groups. Pathogenic bacteria culture was performed after 7 days of drug withdrawal. The negative patients were cured, and the cured patients were treated with nifuratel nysfungin vaginal suppository for consolidation treatment once a week for 6 months. The clinical therapeutic effect in the two groups was recorded. The changes in vaginal microecology and human β-defensin (HβD)-3, interleukin (IL)-1β and IL-8 in vaginal secretions were compared between the two groups before treatment and after 7 days of treatment, and the safety evaluation was carried out. **Results** A total of 268 patients were enrolled in this study, including 136 in the treatment group and 132 in the control group. The mycological cure rates of initial treatment in the treatment group and the control group were 84.56% (115 cases/136 cases) and 73.48% (97 cases/132 cases), respectively; the mycological cure rates of consolidation treatment were 82.61% (95 cases/115 cases) and 70.10% (68 cases/97 cases), respectively; the differences were statistically significant (all $P<0.05$). The proportions of vaginal cleanliness grade Ⅲ-Ⅳ in treatment group and control group after 7 days of treatment were 24.26% and 36.36%; the proportions of vaginal flora density grade Ⅱ-Ⅲ were 79.41% and 68.18%; the proportions of vaginal flora diversity grade Ⅱ-Ⅲ were 77.94% and 65.91%; the proportions of dominant bacteria of *Lactobacillus* were 82.35% and 68.18%; the levels of HβD-3 in vaginal secretions were (129.65±11.51) and (135.87±10.46) pg·mL^{-1}; IL-1β levels were (65.48±9.27) and (72.46±10.38) pg·mL^{-1}; IL-8 levels were (159.36±12.50) and (176.30±13.19) pg·mL^{-1}, and the differences were statistically significant (all $P<0.05$). The total incidence rates of adverse drug reactions in the treatment group and control group were 23.53% (32 cases/136 cases) and 18.38% (25 cases/132 cases), respectively ($P>0.05$). **Conclusion** Compared with nifuratel nysfungin vaginal soft capsule therapy, the combination of vaginal live *Lactobacillus* capsule can improve the vaginal microecology of RVVC patients, and the cure rate of vaginal fungal infection is higher, with better safety.

Key words: vaginal live *Lactobacillus* capsule; nifuratel nysfungin vaginal soft capsule; recurrent vulvovaginal candidiasis; vaginal microecology; intensification; consolidation

外阴阴道念珠菌病(vulvovaginal candidiasis, VVC)是妇科常见病,而其中复发性外阴阴道念珠菌病(recurrent vulvovaginal candidiasis, RVVC)患病率为8%~10%[1]。RVVC作为复杂型VVC,具有治疗难度大、复发率高等特点[2]。研究发现,宿主阴道微生态环境改变导致念珠菌由孢子相转化为菌丝相,可能是RVVC反复发作的重要原因,乳杆菌活菌胶囊与抗真菌药物联合对RVVC行巩固治疗,可降低复发率[3]。但也有研究指出,联合阴道用乳杆菌活菌胶囊治疗并不能使VVC疗效明显升高[4],故该方案仍缺乏足够的临床试验证据。本研究旨在分析阴道用乳杆菌活菌胶囊联合硝呋太尔制霉素阴道软胶囊治疗RVVC患者的临床疗效及安全性。

材料、对象与方法

1 病例选择

2022年1月至2023年5月以本院就诊RVVC患者入选为研究对象。本研究数据经安徽医科大学第二附属医院医学伦理委员会批准公开(伦理批号:YX2024-085)。

诊断与入选标准 符合《阴道微生态评价的临床应用专家共识》[5]中关于RVVC的诊断标准,即1年内有症状性VVC发作≥4次。①阴道分泌物经镜检及沙堡弱琼脂培养基培养均显示念珠菌阳性;②年龄为18~50岁;③有性生活史。

排除标准 ①就诊前1个月内使用免疫抑制药治疗或阴道用药史;②处于妊娠期、哺乳期,巩固治疗期间妊娠;③患有滴虫性阴道病等其他阴道疾病;④合并糖尿病等全身性疾病;⑤合并急慢性肾炎等需要激素治疗的疾病;⑥合并自身免疫性疾病;⑦合并精神分裂症等精神疾病。

2 药品、试剂与仪器

硝呋太尔制霉菌素阴道软胶囊,规格:每盒6粒,批号:21103697,注册证号:国药准字HJ20100044,意

大利 DOPPEL FARMACEUTICI S. R. L. 公司生产;阴道用乳杆菌活菌胶囊,规格:每粒 0.25 g,每粒内含乳杆菌活菌不低于 2.5×10^5 CFU,批号:21114473,批准文号:国药准字 S20030005,内蒙古双奇药业股份有限公司生产。酶联免疫吸附试验试剂盒,均购自深圳晶美生物工程有限公司。

API Candida 酵母鉴定仪,法国生物梅里埃公司产品。

3 分组与治疗方法

将 RVVC 患者根据队列法分为对照组和试验组。对照组患者在睡前将 1 粒硝呋太尔制霉素阴道软胶囊塞入阴道后穹隆,连续治疗 7 d。试验组在对照组治疗的基础上联合阴道用乳杆菌活菌胶囊治疗,在晨起给予阴道用乳杆菌活菌胶囊 0.25 g 阴道局部用药,用药期间避免阴道冲洗,禁止口服广谱抗菌药物及性行为。在治疗后7 d复查阴道病原菌,阴性者为治愈,治愈者参考《阴道微生态评价的临床应用专家共识》[5]进行巩固治疗:硝呋太尔制霉素阴道软胶囊巩固治疗,睡前 1 粒塞入阴道后穹窿,每月 1 次,持续 6 个月。

4 观察指标与疗效评价

阴道微生态 参考《阴道微生态评价的临床应用专家共识》[5],进行阴道分泌物镜检,评估治疗前及治疗 7 d 后阴道清洁度、阴道菌群密集度、阴道菌群多样性、优势菌为乳杆菌检出情况。

阴道分泌物生化检测[6] 在治疗前及治疗后 7 d,指导患者取膀胱截石位,无菌棉棒清洁后置入窥阴器,暴露宫颈,取阴道后穹窿分泌物,酶联免疫吸附试验法检测人 β 防御素(human β-defensin, HβD)-3、白细胞介素(interleukin, IL)-1β、IL-8 水平。

疗效评价 参考《外阴阴道假丝酵母菌病诊治规范修订稿》[7],在治疗 7 d 后评估真菌学治愈率,即念珠菌培养转阴;并在巩固治疗 6 个月完成后的 7 d 再次检测念珠菌培养阴性率,评估巩固治疗情况。

安全性评价 记录外阴灼热、阴道干涩、恶心等药物不良反应发生情况。

5 统计学处理

用 SPSS 24.0 软件进行统计分析。符合正态分布且方差齐性的计量数据用 $\bar{x}\pm s$ 表示,组内比较用配对样本 t 检验,组间比较用独立样本 t 检验;计数资料用率(%)表示,比较用 χ^2 检验比较。

结 果

1 一般资料

本研究共入组 268 例患者,其中试验组 136 例,对照组 132 例。2 组患者年龄、孕次、产次、体质量指数、VVC 病程、阴道分泌物念珠菌菌种分类比较,在统计学上差异均无统计学意义(均 $P>0.05$),组间具有可比性,见表 1。

2 2 组患者阴道微生态的比较

2 组患者治疗 7 d 后与治疗前比较,阴道清洁度Ⅲ~Ⅳ级占比均显著降低,在统计学上差异均有统计学意义(均 $P<0.05$),阴道菌群密集度及阴道菌群多样性Ⅱ~Ⅲ级占比、优势菌为乳杆菌占比均显著升高,在统计学上差异均有统计学意义(均 $P<0.05$);治疗 7 d 后,试验组阴道清洁度Ⅲ~Ⅳ级占比显著低于对照组,在统计学上差异有统计学意义($P<0.05$),阴道菌群密集度及阴道菌群多样性Ⅱ~Ⅲ级占比、优势菌为乳杆菌占比均显著高于对照组,在统计学上差异均有统计学意义(均 $P<0.05$),见表 2。

3 2 组患者阴道分泌物 HβD-3、IL-1β 和 IL-8 表达情况的比较

2 组患者治疗 7 d 后与治疗前比较,阴道分泌物 HβD-3、IL-1β、IL-8 表达水平均降低,在统计学上差异均有统计学意义(均 $P<0.05$);治疗后试验组阴道分泌物 HβD-3、IL-1β、IL-8 表达水平均显著低于对照组,在统计学上差异均有统计学意义(均 $P<0.05$),见表 3。

4 2 组患者的临床疗效评价

试验组与对照组患者治疗 7 d 后念珠菌培养转阴的例数分别为 115 和 97 例,试验组的真菌学治愈率明显高于对照组,在统计学上差异有统计学意义[84.56%(115 例/136 例) *vs* 73.48%(97 例/132 例),$P<0.05$]。试验组 115 例患者完成 6 个月的巩固治疗时,真菌学治愈率为 82.61%(95 例/115 例);对照组 97 例患者完成 6 个月的巩固治疗结束时,真菌学治愈率

表 1 2 组患者一般资料的比较

Table 1 Comparison of general data between the two groups

Item	Control(n=132)	Treatment(n=136)
Age(year, $\bar{x}\pm s$)	32.42±7.09	31.83±6.45
Gravidity(time, $\bar{x}\pm s$)	1.65±0.38	1.59±0.34
Parity(time, $\bar{x}\pm s$)	0.71±0.19	0.68±0.18
Body mass index($kg\cdot m^{-2}$, $\bar{x}\pm s$)	21.33±2.05	21.65±2.14
VVC course(month, $\bar{x}\pm s$)	29.69±5.81	30.45±6.33
Candida species (n, %)		
Candida albicans	104(78.79)	110(80.88)
Candida glabrata	17(12.88)	18(13.24)
Candida tropicalis	6(4.55)	5(3.68)
Candida krusei	5(3.79)	3(2.21)

Control group: Nifuratel nysfungin vaginal soft capsule; Treatment group: Live *lactobacillus* capsule combined with nifuratel nysfungin vaginal soft capsule; WC: Vulvovaginal candidiasis.

表2 2组患者阴道微生态的比较(n, %)

Table 2 Comparison of vaginal microecology between the two groups (n, %)

Item	Control(n=132)		Treatment(n=136)	
	Before treatment	After treatment	Before treatment	After treatment
Vaginal cleanliness				
Grade Ⅰ-Ⅱ	40(30.30)	84(63.64)	39(28.68)	103(75.74)
Grade Ⅲ-Ⅳ	92(69.70)	48(36.36)*	97(71.32)	33(24.26)*#
Vaginal flora density				
Grade Ⅱ-Ⅲ	64(48.48)	90(68.18)*	66(48.53)	108(79.41)*#
No or grade Ⅰ, grade Ⅳ	68(51.52)	42(31.82)*	70(51.47)	28(20.59)*#
Vaginal flora diversity				
Grade Ⅱ-Ⅲ	62(46.97)	87(65.91)*	65(47.79)	106(77.94)*#
No or grade Ⅰ, grade Ⅳ	70(53.03)	45(34.09)*	71(52.21)	30(22.06)*#
Dominant bacteria of *Lactobacillus*				
Yes	64(48.48)	90(68.18)	65(47.79)	112(82.35)
No	68(51.52)	42(31.82)*	71(52.21)	24(17.65)*#

Compared with before treatment in the same group, $^{*}P<0.05$; Compared with control group at the same time, $^{\#}P<0.05$.

表3 2组患者阴道分泌物人β防御素(HβD)-3、白细胞介素(IL)-1β和IL-8的比较($pg \cdot mL^{-1}$, $\bar{x} \pm s$)

Table 3 Comparison of human β-defensin (HβD)-3, interleukin (IL)-1β、IL-8 in vaginal secretion between the two groups ($pg \cdot mL^{-1}$, $\bar{x} \pm s$)

Item	Control(n=132)		Treatment(n=136)	
	Before treatment	After treatment	Before treatment	After treatment
HβD-3	159.23±12.08	135.87±10.46*	161.44±12.79	129.65±11.51*#
IL-1β	166.30±16.38	72.46±10.38*	165.49±14.28	65.48±9.27*#
IL-8	289.46±16.34	176.30±13.19*	291.55±15.43	159.36±12.50*#

Compared with before treatment in the same group, $^{*}P<0.05$; Compared with control group at the same time, $^{\#}P<0.05$.

为70.10%(68例/97例),试验组的巩固治疗真菌学治愈率显著高于对照组,在统计学上差异有统计学意义($P<0.05$)。

5 安全性评价

试验组患者治疗期间发生外阴灼热12例(8.82%)、阴道干涩15例(11.03%)、恶心5例(3.68%);对照组患者发生外阴灼热9例(6.62%)、阴道干涩12例(8.82%)、恶心4例(2.94%);2组患者出现的药物不良反应均为轻微反应,未给予特殊处理均自行好转。试验组和对照组的药物不良反应总发生率组间比较[23.53%(32例/136例) *vs* 18.38%(25例/132例)],在统计学上差异均无统计学意义(均$P>0.05$)。

讨 论

RVVC复发率极高,有报道指出,50%的RVVC患者经抗真菌治疗后在3个月内会复发[8]。硝呋太尔制霉素阴道胶囊是一种复合阴道栓剂,其中硝呋太尔具有广谱抗微生物作用,制霉菌素则对念珠菌具有较强的杀伤力,可用于治疗阴道真菌感染及混合感染[9]。RVVC患者常存在阴道乳酸杆菌明显减少等阴道微生态环境严重失调,导致念珠菌由孢子相转化为菌丝相,被认为是RVVC反复发作的重要因素。乳酸杆菌在健康阴道内占比>80%,可以阻止念珠菌芽管形成、阻断念珠菌黏附于阴道上皮的受体,还能通过形成细菌素、生物活性剂及维持酸性环境等途径抑制念珠菌生长繁殖,故补充阴道乳酸杆菌可能通过改善阴道微生态环境,提升RVVC治疗效果[10]。《阴道微生态评价的临床应用专家共识》[5]指出,正常阴道微生态为阴道菌群密集度Ⅱ~Ⅲ级、阴道菌群多样性Ⅱ~Ⅲ级、优势菌为乳杆菌。本研究在硝呋太尔制霉素阴道软胶囊的基础上联合阴道用乳杆菌活菌胶囊阴道给药,发现治疗后试验组阴道清洁度Ⅲ~Ⅳ级占比低于对照组,阴道菌群密集度及阴道菌群多样性Ⅱ~Ⅲ级占比、优势菌为乳杆菌占比均高于对照组,提示通过阴道给药的方式补充乳酸杆菌能改善RVVC阴道微生态环境。然而,也有学者提出不同意见[11],认为乳酸杆菌并非念珠菌的有效拮抗生物,乳酸杆菌的减少或增多并不能影响RVVC的发作风险及治疗效果。本研究发现,试验组治疗的真菌学治愈率明显高于

对照组(84.56% *vs* 73.48%),表明联合乳杆菌活菌阴道给药可提升 RVVC 治疗效果;考虑与乳酸杆菌形成的生物活性剂等与抗菌药物相似化学物质与硝呋太尔制霉素协同杀灭念珠菌,及乳酸杆菌可在过氧化氢酶的催化下产生次卤酸,增强杀菌效果等有关[12-13]。

HβD-3 为内源性抗菌素肽家族成员之一,广泛表达于女性生殖系统黏膜和妊娠相关组织。在阴道黏膜遭受念珠菌等病原微生物刺激时,Toll 样受体(Toll-like receptor, TLR)活化并诱导 HβD-3 大量产生,HβD-3 不仅能增强单核细胞、巨噬细胞活性及趋化性,也能诱导炎症因子表达增多,放大炎症反应[14-15]。IL-1β、IL-8 则为临床常用炎症指标,二者主要由辅助性 T 细胞(helper T cell, Th)1 分泌,参与 Th1 细胞介导的细胞免疫应答,在病原微生物诱导的急性或慢性感染过程中发挥促进作用[16]。本研究发现,试验组治疗后阴道分泌物 HβD-3、IL-1β、IL-8均显著低于对照组,提示联合乳酸杆菌阴道给药还能促进阴道促炎因子的表达下调,对改善局部免疫功能有利。分析该结果的原因为补充乳酸杆菌可促进念珠菌清除,减轻念珠菌入侵及繁殖诱导的促炎作用,使 HβD-3 等促炎因子在阴道分泌物中表达量下降[17]。另外,由于 RVVC 治疗难度大、复发率高,常需巩固治疗 6 个月,虽然本研究乳酸杆菌阴道给药仅用于初始治疗的 7 d,但试验组巩固治疗真菌学治愈率显著高于对照组(82.61% *vs* 70.10%),考虑与联合阴道用乳杆菌活菌胶囊治疗 7 d 不仅能减轻局部炎症反应,还能改善阴道微生态,提升阴道防御能力,从而提高远期治疗效果[18]。

本研究提示,硝呋太尔制霉素阴道软胶囊联合阴道用乳杆菌活菌胶囊阴道给药治疗 RVVC 可以下调阴道 HβD-3、IL-1β 等促炎因子的表达,有效改善阴道菌群密集度等阴道微生态环境,提高 RVVC 强化及巩固治疗的临床疗效,且不增加药物不良反应,安全可靠。

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