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粪菌移植联合乳果糖对顽固性功能便秘患者胃肠功能、生活质量及心理状态的影响*

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摘要 目的:研究粪菌移植联合乳果糖对顽固性功能便秘患者胃肠功能、生活质量及心理状态的影响。**方法:**选取2016年6月至2018年5月我院消化内科收治的顽固性功能便秘患者100例为研究对象,按照随机数字表法将患者分为对照组($n=45$)和研究组($n=55$)。对照组给予乳果糖口服治疗,研究组则采用粪菌移植联合乳果糖治疗,两组均治疗6周。对比两组临床疗效、胃肠功能以及治疗前后生活质量和心理状态的变化,并观察两组治疗期间不良反应发生情况。**结果:**与对照组比较,研究组总有效率明显升高($P<0.05$)。研究组首次自主排便时间、肛门首次排气时间、肠鸣音恢复时间均短于对照组,胃肠减压引流量高于对照组($P<0.05$)。治疗6周后,两组患者生活质量自评量表(PAC-QOL)评分、Zung焦虑自评量表(SAS)评分和抑郁自评量表(SDS)评分均较治疗前降低,且与对照组比较,研究组PAC-QOL评分、SAS评分、SDS评分均降低($P<0.05$)。两组不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**粪菌移植联合乳果糖对顽固性功能便秘具有较好的疗效,可改善患者胃肠功能和心理状态,同时可提高患者生活质量,无严重不良反应发生。

关键词:粪菌移植;乳果糖;顽固性功能便秘;胃肠功能;生活质量;心理状态

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Effect of Fecal Microbiota Transplantation Combined with Lactulose on Gastrointestinal Function, Quality of Life and Psychological State in Patients with Intractable Functional Constipation*

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ABSTRACT Objective: To study the effects of fecal microbiota transplantation combined with lactulose on gastrointestinal function, quality of life and psychological status in patients with intractable functional constipation. **Methods:** 100 patients with intractable functional constipation who were treated at Gastroenterology Department of our hospital from June 2016 to May 2018 were selected as the research subjects. They were divided into control group ($n=45$) and study group ($n=55$) according to random number table method. The control group was given lactulose orally, while the study group was treated with fecal bacteria transplantation combined with lactulose, and the two groups were treated for 6 weeks. The clinical efficacy, gastrointestinal function and the changes of quality of life and psychological status before and after treatment were compared between the two groups. The adverse reactions of the two groups during treatment were also observed. **Results:** Compared with the control group, the total effective rate of the study group was significantly higher ($P<0.05$). First self defecation time, anus first exhaust time and the recovery time of bowel sounds of the study group were shorter than those of the control group, and gastrointestinal decompression flow rate was higher than that of the control group ($P<0.05$). After treatment, the scores of patients assessment of constipation quality of life (PAC-QOL), Zung's self-rating Anxiety scale (SAS) and self-rating depression scale (SDS) of the two groups were lower than those before treatment, and compared with the control group, the scores of PAC-QOL, SAS and SDS in the study group were significantly decreased ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Fecal microbiota transplantation combined with lactulose has a good effect on intractable functional constipation. It can improve gastrointestinal function and mental state of patients, it can improve the quality of life of patients, and it has no serious adverse reaction.

Key words: Fecal microbiota transplantation; Lactulose; Intractable functional constipation; Gastrointestinal function; Quality of life; Psychological state

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前言

功能性便秘是临床常见的消化系统疾病,其在全球范围内均具有较高的发病率,该病无明显的器质性病变,主要症状表现为排便困难、排便次数减少、粪便干燥等^[1,2]。目前对于功能性便秘的治疗多采用调整饮食习惯和生活方式、生物反馈或者药物进行治疗,但是部分功能性便秘患者经上述治疗无明显效果,且症状持续加重,因此,此类功能性便秘被称为顽固性功能便秘^[3-5]。顽固性功能便秘治疗难度大、复发率高,对患者的心理状态和生活质量均造成严重影响^[6]。乳果糖是治疗顽固性功能便秘的常用泻药,其经口服后可在患者体内形成酸性环境,有利于肠道内乳酸菌的生长和繁殖,从而加速了肠道蠕动,进而促进食物的快速消化^[7]。然而,有研究显示^[8],单纯服用乳果糖效果并不明显,需与其他药物联合使用才具有良好的临床疗效。粪菌移植是近年来兴起的用于治疗顽固性功能便秘的主要方法,是指将健康供体的功能菌群通过一定的方式植入便秘患者肠道内,以重建患者肠道微生态平衡,从而达到治疗便秘的目的^[9,10]。本研究通过分析粪菌移植联合乳果糖对顽固性功能便秘患者胃肠功能、生活质量及心理状态的影响,以期为临床治疗提供数据支持,结果阐述如下。

1 资料与方法

1.1 一般资料

选取2016年6月至2018年5月我院消化内科收治的顽固性功能便秘患者100例为研究对象,纳入标准:(1)所有患者均符合功能性便秘的Rome III诊断标准^[11];(2)便秘症状持续加重,并经饮食和生活方式干预以及灌肠、药物治疗无效者;(3)治疗前一个月内未使用过微生态制剂者;(4)自愿参与本研究并签署知情同意书者。排除标准:(1)器质性或药物引起的便秘者;(2)伴有甲状腺功能减退、甲状腺功能亢进、糖尿病等影响胃肠运动功能的代谢性疾病者;(3)严重的心肝肾功能不全者;(4)孕妇或哺乳期女性。将入选患者按照随机数字表法分为研究组($n=55$)和对照组($n=45$)。研究组男性30例,女性25例;年龄60-79岁,平均 (68.65 ± 6.98) 岁;体质量指数 $19-26 \text{ kg/m}^2$,平均 $(22.63 \pm 2.55) \text{ kg/m}^2$;病程1-25年,平均 (11.68 ± 5.28) 年;便秘类型:慢性传输型便秘10例,出口梗阻型便秘6例,混合型便秘39例。对照组男性24例,女性21例;年龄61-75岁,平均 (67.20 ± 5.23) 岁;体质量指数 $18-27 \text{ kg/m}^2$,平均 $(21.26 \pm 2.09) \text{ kg/m}^2$;病程1-23年,平均 (10.29 ± 5.66) 年;便秘类型:慢性传输型便秘8例,出口梗阻型便秘5例,混合型便秘32例。两组患者在年龄构成、性别比例、体质量指数、便秘类型等方面比较差异不显著($P>0.05$),均衡可比。本研究符合我院伦理委员会的相关规定。

1.2 方法

1.2.1 粪菌液的制备 粪菌供体纳入标准:①年龄 <60 岁,具有良好的饮食习惯及生活方式;②近6个月未应用微生态制剂、抗生素及其他药物;③无传染病史;④既往无慢性病(如便秘、肠易激综合征、炎症性肠病)、无自身免疫病、恶性肿瘤以及消化系统手术史;⑤目前无消化道症状;⑥粪便常规无异常,幽门螺杆菌、痢疾杆菌等粪便微生物检测为阴性;⑦无神经精神

系统疾病。收集健康粪菌供体的新鲜粪便80-100g,放入无菌搅拌器内,并加入500mL生理盐水充分搅拌均匀,随后在过滤网(孔径依次为2.0mm、0.5mm)的作用下将大颗粒物质、未吸收的食物残渣以及细小物质等杂质过滤掉,过滤完成后,采用3500转/min的速率将粪菌液离心15min,并将离心后的粪菌液保存于4℃的冰箱中,以上所有操作需在2h内完成。

1.2.2 治疗方法 对照组给予乳果糖口服液(北京韩美药品有限公司,国药准字:H20065730,规格:100mL:66.7g)治疗,剂量为30mL,每天早晨服用1次;研究组在口服乳果糖的基础上加用粪菌移植治疗,经胃镜给药,每隔4天1次,共3次,每次400mL粪菌液,粪菌移植后0.5h内尽量避免排便,给药当天停用乳果糖,其余时间正常服用。两组疗程均为6周,且治疗期间两组均停用其他通便药。

1.3 观察指标

1.3.1 疗效评价 显效:无排便困难,自主排便次数不小于3次/周,Bristol粪便性状为4-6级;有效:排便困难程度较治疗前有所改善,自主排便次数不小于3次/周,Bristol粪便性状为2-3级;无效:排便困难程度较治疗前无改善,自主排便次数小于3次/周,Bristol粪便性状为1-2级。总有效率为显效例数和有效例数之和与总例数的比值^[12]。

1.3.2 胃肠功能 包括首次自主排便时间、肛门首次排气时间、肠鸣音恢复时间、胃肠减压引流量。

1.3.3 生活质量^[13] 于治疗前和治疗6周后采用便秘患者生活质量自评量表(PAC-QOL)评价患者生活质量,该量表共4个部分(生理、心理、担心焦虑以及满意度),包括28个条目,采用5级评分法,得分越低表示生活质量越好。

1.3.4 心理状态 于治疗前和治疗6周后分别采用Zung焦虑自评量表(SAS)和抑郁自评量表(SDS)评价患者的焦虑和抑郁程度,两个量表均为20个条目,采用4级评分法,总分为20个条目得分 $\times 1.25$,得分越高表示焦虑或抑郁越严重^[14]。

1.3.5 不良反应 观察两组治疗期间的不良反应发生情况。

1.4 统计学方法

应用SPSS19.0统计学软件进行统计分析。有效率等计数资料用百分数表示,采用卡方检验,胃肠功能、生活质量、心理状态指标等计量资料采用均数 $\pm$ 标准差表示,采用t检验,将 $\alpha=0.05$ 设为检验标准。

2 结果

2.1 两组治疗疗效比较

与对照组比较,研究组总有效率明显升高($P<0.05$)。见表1。

2.2 两组胃肠功能比较

与对照组比较,研究组首次自主排便时间、肛门首次排气时间、肠鸣音恢复时间均变短,胃肠减压引流量则升高($P<0.05$)。见表2。

2.3 两组生活质量和心理状态比较

治疗前,两组PAC-QOL评分、SAS评分、SDS评分比较差异无统计学意义($P>0.05$);治疗6周后,两组PAC-QOL评分、SAS评分、SDS评分均较治疗前降低($P<0.05$),且与对照组比较,研究组PAC-QOL评分、SAS评分、SDS评分均降低($P<0.05$)。见表3。

表 1 两组治疗疗效比较[n(%)]

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

Groups	n	Excellence	Effective	Invalid	Total effective rate
Study group	55	21(38.18)	27(49.09)	7(12.73)	48(87.27)
Control group	45	14(31.11)	16(35.56)	15(33.33)	30(66.67)
χ^2					6.124
<i>P</i>					0.013

表 2 两组胃肠功能比较($\bar{x} \pm s$)Table 2 Comparison of gastrointestinal function of two groups($\bar{x} \pm s$)

Groups	n	First self defecation time (d)	Anus first exhaust time (h)	Recovery time of bowel sounds(d)	Gastrointestinal decompression flow rate(ml/d)
Study group	55	2.58± 0.16	11.26± 2.98	1.98± 0.56	765.25± 50.36
Control group	45	4.12± 0.86	24.06± 2.36	3.89± 0.83	569.38± 40.92
<i>t</i>		13.022	23.419	13.685	21.463
<i>P</i>		0.000	0.000	0.000	0.000

表 3 两组生活质量和心理状态比较($\bar{x} \pm s$, 分)Table 3 Comparison of the quality of life and psychological status in the two groups($\bar{x} \pm s$, scores)

Groups	n	PAC-QOL score		SAS score		SDS score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	55	115.36± 18.06	59.22± 19.38 [#]	60.98± 8.20	40.53± 5.23 [#]	60.11± 7.25	39.89± 6.02 [#]
Control group	45	114.98± 19.34	79.58± 25.33 [#]	61.06± 7.57	45.28± 6.84 [#]	59.14± 6.58	46.25± 5.14 [#]
<i>t</i>		0.101	4.553	0.050	3.934	0.694	5.608
<i>P</i>		0.919	0.000	0.960	0.000	0.490	0.000

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

2.4 两组不良反应比较

治疗期间, 研究组患者在粪菌移植后有 2 例出现恶心、腹胀、排气增多、腹泻, 两天之后, 以上症状消失, 不良反应发生率为 3.64%(2/55); 对照组患者服药后有 2 例出现恶心、腹胀, 但患者可耐受, 两周之后症状消失, 不良反应发生率为 4.44%(2/45), 两组不良反应发生率比较差异无统计学意义($\chi^2=0.042$, *P*=0.837)。

3 讨论

顽固性功能便秘是一种起病缓慢、病因复杂、复发率高的慢性疾病, 此类疾病大多是由于患者生活或工作压力大、不合理的饮食习惯和生活方式以及滥用药物等因素引起^[15,16]。老年患者由于身体机能下降, 肠道内的水分相较于年轻人明显减少, 肠道蠕动频率也相应降低, 导致粪便干燥结块, 因此老年人更易发生顽固性功能便秘^[17,18]。顽固性功能便秘治疗难度高, 患者精神负担重, 从而导致此类患者多伴有不同程度的心理疾病, 常表现为焦虑和抑郁, 严重影响患者生活质量^[19,20]。已有研究表明^[21-23], 便秘患者粪便菌群将发生特征性改变, 多存在肠道菌群紊乱现象, 具体表现为真菌、需氧菌、大肠杆菌等潜在致病菌相对增多而专性厌氧菌则相对减少, 肠道菌群的变化将影响患者胃肠功能, 因此, 寻找一种可以纠正便秘患者肠道菌

群的治疗方法显得尤为重要。

本研究中, 研究组采用粪菌移植联合乳果糖以治疗顽固性功能便秘, 与单纯使用乳果糖治疗相比, 研究组总有效率明显升高(*P*<0.05), 同时, 与对照组比较, 研究组首次自主排便时间、肛门首次排气时间、肠鸣音恢复时间均变短, 胃肠减压引流量则升高(*P*<0.05), 提示粪菌移植联合乳果糖可以提高顽固性功能便秘的治疗效果, 改善患者的胃肠功能。分析原因为通过粪菌移植, 将增加患者肠道内的益生菌, 而益生菌可以在患者肠道黏膜上形成一道生物屏障, 从而可以复活机体的免疫功能和提高抗感染能力, 进而能够重建肠道菌群, 改善患者胃肠功能, 最终提高了治疗效果^[24-26]。另外, 本研究结果还显示, 治疗后, 两组 PAC-QOL 评分、SAS 评分、SDS 评分均较治疗前降低, 且与对照组比较, 研究组 PAC-QOL 评分、SAS 评分、SDS 评分更低(*P*<0.05)。说明两种治疗方法均可以改善患者的心理状态, 提高患者生活质量, 但粪菌移植联合乳果糖改善效果更明显。现代医学认为, 便秘是一种身心疾病, 便秘症状的持续加重将引发患者焦虑、抑郁等心理状态的出现, 反之, 存在心理异常的便秘患者, 其便秘症状也将随着异常心理的发展而逐渐加重^[27,28]。因此, 在便秘治疗过程中, 应关注患者情绪的变化, 不断调整其面对疾病的心态, 并采取合理的治疗方式以提高治疗效果, 从而减少患者的心理压力, 进而提高生活质量。联合用药的

使用,能比较快速地纠正患者体内的菌群混乱现象,改善患者便秘症状,起效快,因此可以增强患者对疾病治疗的信心^[29,30]。此外,治疗期间两组不良反应发生率比较差异无统计学意义($P>0.05$),说明粪菌移植并不会加重患者的不良反应。另外,粪菌移植联合乳果糖作为一种新兴的治疗方法,还存在一些不足之处,例如便秘作为一种慢性疾病,本研究未对患者进行长时间的随访观察,同时粪菌液的制备、供体的选择等均无统一规范的措施,因此在后续的研究中应加强随访以及加强粪菌液制备过程的规范。

综上所述,与单纯的采用乳果糖治疗相比,粪菌移植联合乳果糖治疗顽固性功能便秘效果更佳,其可改善患者的胃肠功能和心理状态,提高患者生活质量,但远期疗效需进一步随访验证。

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