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酪酸梭菌活菌胶囊联合四联疗法对幽门螺杆菌阳性胃溃疡患者血清炎症因子、胃肠激素和胃蛋白酶原亚群的影响*

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摘要 目的:探讨酪酸梭菌活菌胶囊联合四联疗法对幽门螺杆菌(*Hp*)阳性胃溃疡患者血清炎症因子、胃肠激素和胃蛋白酶原亚群的影响。**方法:**选择天津市中医药研究院附属医院于2017年2月~2020年3月期间收治的*Hp*阳性胃溃疡患者100例,按信封抽签法随机分为对照组(50例,采用四联疗法治疗)、观察组(50例,采用酪酸梭菌活菌胶囊联合四联疗法治疗)。对比两组患者疗效、血清炎症因子、胃肠激素、胃蛋白酶原亚群、*Hp*根除率及不良反应。**结果:**治疗4周后,观察组患者的总有效率为92.00%(46/50),高于对照组患者的70.00%(35/50)($P<0.05$)。观察组治疗4周后白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)、降钙素原(PCT)、C反应蛋白(CRP)水平低于对照组($P<0.05$)。观察组治疗4周后胃泌素(GAS)低于对照组,胃动素(MTL)高于对照组($P<0.05$)。观察组治疗4周后胃蛋白酶原I(PG I)、胃蛋白酶原II(PG II)水平较对照组更低($P<0.05$)。对比两组不良反应发生率无差异($P>0.05$)。观察组的*Hp*根除率为94.00%(47/50),较对照组的72.00%(36/50)更高($P<0.05$)。**结论:**酪酸梭菌活菌胶囊联合四联疗法治疗*Hp*阳性胃溃疡患者,可取得显著疗效,提高*Hp*根除率,改善血清炎症因子、胃肠激素和胃蛋白酶原亚群,且安全性较好。

关键词:酪酸梭菌活菌胶囊;四联疗法;幽门螺杆菌阳性;胃溃疡;炎症因子;胃肠激素;胃蛋白酶原亚群

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Effect of *Clostridium Butyricum* Capsule Combined with Quadruple Therapy on Serum Inflammatory Factors, Gastrointestinal Hormones and Progastrin Subsets in Patients with *Helicobacter Pylori* Positive Gastric Ulcer*

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ABSTRACT Objective: To investigate the effect of *clostridium butyricum* capsule combined with quadruple therapy on serum inflammatory factors, gastrointestinal hormones and progastrin subsets in patients with *Helicobacter pylori* (*HP*) positive gastric ulcer. **Methods:** 100 cases of *HP* positive gastric ulcer patients who were admitted in Affiliated Hospital of Tianjin Institute of Traditional Chinese Medicine from February 2017 to March 2020 were selected, they were randomly divided into control group (50 cases, treated with quadruple), observation group (50 cases, treated with *clostridium butyricum* capsule combined with quadruple) by envelope lottery method. The efficacy, serum inflammatory factors, gastrointestinal hormones, progastrin subsets, *Hp* eradication rate and adverse reactions of patients in the two groups were compared. **Results:** After 4 weeks of treatment, the total effective rate of patients in the observation group was 92.00% (46 / 50), which was higher than 70.00% (35 / 50) of patients in the control group ($P<0.05$). The levels of interleukin-6 (IL-6), tumor necrosis factor - α (TNF- α), procalcitonin (PCT), C-reactive protein (CRP) in the observation group were lower than those of the control group after 4 weeks of treatment ($P<0.05$). The levels of gastrin (GAS), motilin (MTL) in the observation group were lower than those of the control group after 4 weeks of treatment ($P<0.05$). The levels of pepsinogen I (PG I) and pepsinogen II (PG II) in the observation group were lower than those of the control group after 4 weeks of treatment ($P<0.05$). There was no difference in incidence rate of adverse reactions between the two groups ($P>0.05$). The 94.00% (47/50) of *Hp* eradication rate in the observation group was higher than 72.00% (36/50) of the control group. **Conclusion:** *Clostridium butyricum* capsule combined with quadruple therapy in the treatment of *Hp* positive gastric ulcer patients, can achieve significant curative effect, improve *HP* eradication rate, improve serum inflammatory factors, gastrointestinal hormones and progastrin subsets, and has good safety.

Key words: *Clostridium butyricum* capsule; Quadruple therapy; *Helicobacter pylori* positive; Gastric ulcer; Inflammatory factors; Gastrointestinal hormones; Progastrin subgroup

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前言

胃溃疡是脾胃科常见病,可由各种致病因素的刺激下引发,发病时出现胃黏膜损坏,继而引起粘膜脱落,导致炎症,该病存在致病菌易感人群,极易复发。胃溃疡的主要临床症状包括腹胀、上腹痛、恶心、反酸、呕吐等,严重者可引发穿孔、消化道出血、癌变等并发症,危及患者性命^[1-3]。胃溃疡的发病原因较多,包括幽门螺杆菌(*Hp*)感染、心理应激反应、饮食因素等,其中以 *Hp* 感染最为常见^[4,5]。埃索美拉唑四联疗法是临床治疗 *Hp* 阳性胃溃疡的常用方案,可获得一定治疗效果,但部分患者对此方案并不敏感,治疗效果不佳,这对患者预后的改善造成影响^[6,7]。微生物制剂的研发给患者带来福音,目前临床上已将其用于治疗 *Hp* 阳性胃溃疡,并取得了一定的成效。本研究对天津市中医药研究院附属医院收治的部分 *Hp* 阳性胃溃疡患者给予酪酸梭菌活菌胶囊联合四联疗法治疗,观察其疗效,旨在为临床治疗该病提供一定的依据。

1 资料与方法

1.1 临床资料

选择天津市中医药研究院附属医院于 2017 年 2 月~2020 年 3 月期间收治的 *Hp* 阳性胃溃疡患者 100 例。纳入标准:(1)研究获得天津市中医药研究院附属医院伦理委员会同意;(2)诊断参考《内科学》^[8],行 14 C 尿素呼气试验并确认为 *Hp* 感染阳性;(3)精神正常,无认知功能障碍;(4)入组前 1 个月内未接受胃酸抑制剂、抗生素等药物的治疗;(5)年龄 ≥ 20 岁者;(6)对本研究知情并签署同意书。排除标准:(1)依从性差,难以遵从医嘱用药者;(2)对本研究用药禁忌者;(3)合并心肝肾等脏器功能不全者;(4)存在胃肠道手术史者;(5)妊娠期或哺乳期女性;(6)合并恶性肿瘤者。按信封抽签法将患者分为对照组($n=50$)、观察组($n=50$)。对照组男 30 例,女 20 例,平均年龄(43.89 ± 4.61)岁,平均病程(2.35 ± 0.87)年,平均溃疡直径(10.84 ± 1.81)mm,平均体质指数(23.64 ± 1.27)kg/m²。观察组男 31 例,女 19 例,平均年龄(44.51 ± 5.36)岁,平均病程(2.42 ± 0.96)年,平均溃疡直径(11.97 ± 1.92)mm,平均体质指数(23.95 ± 1.36)kg/m²。对比两组一般资料无差异($P>0.05$),具有可比性。

1.2 方法

给予对照组四联疗法,具体如下:埃索美拉唑镁肠溶片(江西山香药业有限公司,国药准字 H20203298,规格:按 C₁₇H₁₉N₃O₅S 计 20 mg)口服,20 mg/次,2 次/d;阿莫西林胶囊(上海衡山药业有限公司,国药准字 H31021098,规格:按 C₁₆H₁₉N₃O₅SS 计 0.25 g)口服,10 mg/次,2 次/d;克拉霉素胶囊

(上海普康药业有限公司,国药准字 H20067096,规格:0.125 g)口服,500 mg/次,2 次/d;枸橼酸铋钾[济南恒基制药有限公司,国药准字 H20003101,规格:每粒含枸橼酸铋钾 0.3 g(以铋计 110 mg)]口服,60 mg/次,2 次/d。观察组采用四联疗法联合酪酸梭菌活菌胶囊(重庆泰平药业有限公司,国药准字 S20040054,规格:每粒胶囊含药粉 0.2 g,有效期内含活酪酸梭菌 $\geq 5 \times 10^7$ CFU/g,每粒胶囊内含活酪酸梭菌 $\geq 1 \times 10^7$ CFU)治疗,四联疗法用药方案同对照组,酪酸梭菌活菌胶囊口服,400 mg/次,3 次/d。两组均连续治疗 4 周。

1.3 观察指标

(1)比较两组治疗总有效率、*Hp* 根除率及不良反应发生率,14 C 尿素呼气试验检测结果呈阴性则提示 *Hp* 根除。(2)采集患者清晨空腹外周静脉血液,采血时间治疗前、治疗 4 周后,血液样本经离心处理(3100 r/min 离心 13 min,离心半径 14 cm),分离血清后置于冰箱中待测。白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)、降钙素原(PCT)、C 反应蛋白(CRP)以及胃蛋白酶原 I (PG I)、胃蛋白酶原 II (PG II)采用酶联免疫吸附法检测,胃泌素(GAS)、胃动素(MTL)采用放射免疫法检测,试剂盒购自南京森贝伽生物技术有限公司,按照试剂盒说明书严格操作。

1.4 疗效评定标准

显效:胃镜检查溃疡面积减少超过 75%,症状、体征基本消失;有效:患者症状显著改善,溃疡数量减少 50%~75%;无效:溃疡面积减少不足一半,症状、体征较治疗前无明显改善或有加重趋势。总有效率 = 显效率 + 有效率^[9]。溃疡面积计算^[10]:经溃疡中心测量横径与纵径,面积 = (最大纵径/2) × (最大横径/2) × π 。

1.5 统计学方法

使用 SPSS20.0 软件分析数据。计数资料以百分数表示,组间比较采用卡方检验。计量资料均为符合正态分布的连续变量,使用均数 $\pm$ 标准差表示,行 *t* 检验,检验水平为 $\alpha=0.05$ 。

2 结果

2.1 两组近期疗效对比

治疗 4 周后,观察组患者的总有效率为 92.00%(46/50)高于对照组患者的 70.00%(35/50),两组患者的疗效差异有统计学意义($P<0.05$)。见表 1。

2.2 两组炎症因子比较

对比治疗前两组炎症因子无差异($P>0.05$);对比治疗前,治疗 4 周后两组 IL-6、TNF- α 、PCT、CRP 均下降($P<0.05$);观察组治疗 4 周后 IL-6、TNF- α 、PCT、CRP 水平低于对照组($P<0.05$)。见表 2。

表 1 两组近期疗效对比 例(%)

Table 1 Comparison of short-term efficacy between the two groups n(%)

Groups	Obvious effect	Effective	Invalid	Total efficiency
Control group (n=50)	12(24.00)	23(46.00)	15(30.00)	35(70.00)
Observation group(n=50)	19(38.00)	27(54.00)	4(8.00)	46(92.00)
χ^2				7.862
<i>P</i>				0.005

表 2 两组炎症因子($\bar{x} \pm s$)Table 2 Inflammatory factors in two groups($\bar{x} \pm s$)

Groups	Time points	IL-6(ng/L)	TNF- α (g/L)	PCT(μ g/L)	CRP(mg/L)
Control group (n=50)	Before treatment	24.19 $\pm$ 2.65	1.82 $\pm$ 0.37	0.85 $\pm$ 0.17	8.44 $\pm$ 0.46
	After 4 weeks of treatment	17.87 $\pm$ 1.74*	1.36 $\pm$ 0.32*	0.68 $\pm$ 0.13*	6.15 $\pm$ 0.27*
Observation group (n=50)	Before treatment	24.24 $\pm$ 2.26	1.78 $\pm$ 0.46	0.89 $\pm$ 0.14	8.49 $\pm$ 0.55
	After 4 weeks of treatment	12.20 $\pm$ 1.86**	0.96 $\pm$ 0.25**	0.47 $\pm$ 0.16**	4.28 $\pm$ 0.34**

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

2.3 两组胃肠激素指标比较

两组治疗前胃肠激素对比无差异($P > 0.05$);对比治疗前, 治疗 4 周后两组 GAS 更低, MTL 更高 ($P < 0.05$), 且观察组

两组治疗前 GAS 较对照组更低, MTL 较对照组更高 ($P < 0.05$)。见表 3。

表 3 两组胃肠激素指标比较($\bar{x} \pm s$, ng/L)Table 3 Comparison of gastrointestinal hormone indexes between the two groups($\bar{x} \pm s$, ng/L)

Groups	Time points	GAS	MTL
Control group (n=50)	Before treatment	142.37 $\pm$ 15.10	332.40 $\pm$ 24.91
	After 4 weeks of treatment	115.61 $\pm$ 14.87*	429.86 $\pm$ 23.75*
Observation group(n=50)	Before treatment	141.85 $\pm$ 14.98	331.36 $\pm$ 22.50
	After 4 weeks of treatment	93.78 $\pm$ 12.74**	515.11 $\pm$ 19.24**

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

2.4 两组胃蛋白酶原亚群比较

两组治疗前 PG I、PG II 对比组间无差异($P > 0.05$);对比治

疗前,治疗 4 周后两组 PG I、PG II 更低 ($P < 0.05$),且观察组较

对照组更低 ($P < 0.05$);见表 4。

表 4 两组胃蛋白酶原亚群比较($\bar{x} \pm s$, μ g/L)Table 4 Comparison of pepsinogen subsets between the two groups($\bar{x} \pm s$, μ g/L)

Groups	Time points	PG I	PG II
Control group (n=50)	Before treatment	187.48 $\pm$ 16.81	32.07 $\pm$ 2.16
	After 4 weeks of treatment	127.10 $\pm$ 21.93*	24.94 $\pm$ 2.31*
Observation group(n=50)	Before treatment	186.95 $\pm$ 20.86	32.15 $\pm$ 3.14
	After 4 weeks of treatment	83.95 $\pm$ 17.97**	19.78 $\pm$ 2.09**

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

2.5 两组 Hp 根除率比较

经 4 周治疗后,对两组行 14 C 尿素呼气试验。结果显示,对照组、观察组阴性人数分别为 36 例、47 例,从而可得对照组、观察组 Hp 根除率分别为 72.00%(36/50)、94.00%(47/50),显然,观察组的 Hp 根除率较对照组更高($\chi^2=8.575, P=0.003$)。

2.6 不良反应

治疗期间,对照组出现腹胀气、呕吐、头晕各 1 例,不良反应发生率为 6.00%(3/50);观察组出现腹胀气、呕吐各 1 例,头晕 2 例,不良反应发生率为 8.00%(4/50);两组不良反应发生率无差异($\chi^2=0.154, P=0.695$)。

3 讨论

胃溃疡属消化系统疾病,有相关文献表明人群中约有 10% 曾存在胃溃疡发病,该病在临床上较为常见^[11]。目前,胃溃疡的致病机制已基本明确, Hp 感染是胃溃疡的主要致病因素之一,

Hp 传播途径极其简单,因其对传染对象要求极低,故具有较强的传染性^[12,13]。通常情况下, Hp 可在酸性环境下生长,与高胃酸共同作用促进胃腔炎症的发生,胃炎可损坏胃组织,造成胃溃疡^[14,15]。临床研究也证实^[16]胃溃疡患者中检测出 Hp 感染的概率比普通人群高很多。因此,不断提升 Hp 根除率,能从根源上治愈胃溃疡,改善患者的诸多症状,现已成为临床上治疗胃溃疡方面的重要标杆之一。现阶段,临床上治疗 Hp 感染胃溃疡的基础药物为质子泵抑制剂,埃索美拉唑四联疗法作为治疗该病的常用方法,其中埃索美拉唑能够发挥抑制胃分泌胃酸的作用,从而阻碍胃内酸环境的快速形成,并且在此基础上,联合阿莫西林、克拉霉素等抗菌谱较广、抑菌作用明显的抗生素,可显著的促进胃内环境的改善,达到有效清除 Hp 的作用^[17]。另外,在治疗上联合枸橼酸铋钾,可发挥枸橼酸铋钾与溃疡表面的亲和作用,从而创建一个隔离层,构建一层保护膜,由此阻碍胃酸对胃黏膜的进一步损伤,达到保护胃黏膜的功效,同时,枸橼酸

铋钾可促进胃肠黏膜上皮细胞分泌黏液,促进上皮细胞修复,有助于Hp的根除^[18]。虽然四联疗法具有较好的临床疗效,但同时也存在一定的不足,如不少常用于Hp感染的抗菌药物其耐药率处于上升趋势;抗菌药物易引起消化道不良反应^[19]。因此,找寻疗效更显著、Hp根除率更高的治疗方法对于临床上更有效的诊治该病具有极其重要的意义。近年研究发现^[20]联合微生态制剂用于Hp胃溃疡治疗,有望进一步提高疗效,逐渐引起临床重视。

在治疗多种肠道疾病上,相比于其他微生态制剂,酪酸梭菌活菌制剂能表现出更好的治疗效果。此次研究在四联疗法的基础上联合酪酸梭菌活菌胶囊治疗Hp胃溃疡,结果显示,酪酸梭菌活菌胶囊联合四联疗法可提高Hp根除率,取得显著疗效。究其原因,临床中常用的抗菌药物在胃部环境中的活性较低,且无法直接穿透黏液层作用于病原菌。而酪酸梭菌活菌胶囊活性较高,能够与肠道内的益生菌共存,有效纠正胃肠道微生态失衡^[21,22]。有研究表明^[23],酪酸梭菌活菌胶囊可在胃内形成一个低pH环境,究其原因,为在发挥药效的过程中,可生成短链脂肪酸,从而营造酸性胃环境,抑制胃溃疡致病菌的繁殖,进而阻止Hp定植于胃黏膜。酪酸梭菌还可通过分泌大量免疫球蛋白,提高机体免疫力,从而提高Hp根除率。进一步观察实验指标发现,酪酸梭菌活菌胶囊联合四联疗法治疗可有效改善Hp胃溃疡患者血清炎症因子、胃肠激素和胃蛋白酶原亚群水平。GAS具有强大的刺激胃酸分泌的效应,当胃黏膜受损时,其水平迅速升高^[24]。MTL的主要作用是刺激胃肠道和胆道的运动,可促进胃排空^[25]。PG是反应胃黏膜状态较为可靠的血清学指标,血清PG I、PG II的水平高低与胃黏膜腺体细胞的功能状况有关,在一定程度上能反应出机体胃黏膜的状态好坏^[26]。而IL-6、TNF- α 、PCT、CRP等炎症因子可通过促进淋巴细胞分化和抗体产生,参与胃黏膜的受损进程^[27]。以往有研究结果证实IL-6水平与Hp阳性感染严重程度呈正相关^[28]。酪酸梭菌活菌胶囊可通过分泌和释放丁酸,修复受损的肠黏膜,并抑制炎症因子分泌和腐败菌的滋生,从而改善胃肠道环境^[29,30]。同时在本研究治疗过程中,两组不良反应发生率组间对比无差异,然而,临床也有实践证表明酪酸梭菌活菌胶囊的某些菌株可引起食物中毒等不良反应,故而在治疗期间用药仍需多加注意,其联合用药的安全性有待进一步扩大样本量的研究加以验证。

综上所述,在四联疗法基础上配合酪酸梭菌活菌胶囊应用于临床治疗Hp阳性胃溃疡患者,安全性较好,可取得显著疗效与较高的Hp根除率,其具体作用机制可能与降低血清炎症因子水平,调节胃肠激素和胃蛋白酶原亚群水平有关。

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