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中药止血粉联合止血后口服桃仁承气汤对上消化道出血小鼠的治疗效果及相关机制研究 *

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摘要 目的:探讨与研究中药止血粉联合止血后口服桃仁承气汤对上消化道出血小鼠的治疗效果及相关机制。**方法:**C57 野生型雄性小鼠 24 只随机平分为三组 - 模型组、止血组、联合组,三组建立了应激性消化道出血模型。建模后 2 周联合组给予中药止血粉联合口服桃仁承气汤治疗,止血组给予中药止血粉治疗,模型组给予等剂量的生理盐水治疗。**结果:**实验过程中所有小鼠都存活,止血组、联合组治疗第 2 周与第 4 周的体重高于模型组(P<0.05),联合组高于止血组(P<0.05)。止血组、联合组治疗第 2 周与第 4 周的血清白介素(Interleukin,IL)-6 与 IL-8 表达水平低于模型组(P<0.05),联合组低于止血组(P<0.05)。止血组、联合组治疗第 2 周与第 4 周的消化道溃疡出血指数对比都低于模型组(P<0.05),联合组低于止血组(P<0.05)。止血组、联合组治疗第 2 周与第 4 周的胃上皮组织核因子 κB(nuclear factor kappa-B,NF-κB)、Caspase-3 蛋白相对表达水平低于模型组(P<0.05),联合组低于止血组(P<0.05)。**结论:**中药止血粉联合止血后口服桃仁承气汤在应激性消化道出血小鼠中的应用能减轻消化道组织损伤,抑制炎症因子的表达,促进小鼠正常发育,其作用机制可能与抑制 NF-κB、Caspase-3 蛋白表达有关。

关键词:中药止血粉;桃仁承气汤;上消化道出血;小鼠;核因子 κB;白介素 -6
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Study on Therapeutic Effect and Related Mechanisms of Chinese Medicine Hemostatic Powder Combined with Hemostasis and Oral Administration of Taoren Chengqi Decoction on Mice with Upper Gastrointestinal Hemorrhage*

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ABSTRACT Objective: To explore and study the therapeutic effects and related mechanisms of Chinese medicine hemostatic powder combined with hemostasis after oral administration of Taoren Chengqi Decoction on mice with upper gastrointestinal bleeding. **Methods:** 24 cases of C57 wild-type male mice were randomly divided into three groups-model group, hemostatic group, and combined group. The three groups established a stress gastrointestinal bleeding model. At two weeks after modeling, the combined group were treated with traditional Chinese medicine hemostatic powder combined with oral Taoren Chengqi Decoction, the hemostatic group were treated with traditional Chinese medicine hemostatic powder, and the model group were treated with the same dose of normal saline. **Results:** All mice were survived during the experiment. The body weight of the hemostatic group and the combined group were higher than the model group in the 2nd and 4th weeks of treatment (P<0.05), and the combined group were higher than the hemostatic group (P<0.05). The expression levels of serum interleukin (IL)-6 and IL-8 in the hemostasis group and the combination group were lower than the model group in the 2nd and 4th weeks of treatment (P<0.05) , and the combined group were lower than the hemostatic group (P<0.05). The bleeding index of peptic ulcer in the hemostatic group and the combined group were lower than the model group in the 2nd week and the 4th week of treatment (P<0.05), and the combined group were lower than the hemostatic group (P<0.05). The relative expression levels of nuclear factor kappa-B (NF-κB) and Caspase-3 protein in gastric epithelial tissues in the hemostasis group and the combined group were lower than the model group in the 2nd week and the 4th week of treatment(P<0.05), The combined group were lower than the hemostatic group (P<0.05). **Conclusion:** The application of Chinese medicine hemostatic powder combined with hemostasis after oral administration of Taoren Chengqi Decoction in mice with stress gastrointestinal bleeding can reduce gastrointestinal tissue damage,

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inhibit the expression of inflammatory factors, and promote the normal development of mice. Its mechanism action may be related to inhibit NF-κB and Caspase-3 protein expression.

Key words: Traditional Chinese Medicine Hemostatic Powder; Taoren Chengqi Decoction; Upper Gastrointestinal Bleeding; Mice; Nuclear Factor κB; Interleukin-6

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前言

当前上消化道出血在吸烟、饮酒、大量服用非甾体类抗炎药人群中有很高的发生率,且治疗费用逐年增加[1]。其中应激性消化道出血为消化道出血的主要类型,是指由应激因素引起的一种以炎性糜烂、胃肠道出血、浅表溃疡为特征的急性胃黏膜病变[2,3]。当前治疗应激性消化道出血主要是以质子泵抑制剂或(和)铋剂为基础,合并 2 种抗生素组成的三联 / 四联疗法,虽然有一定的效果,但是很多患者存在耐药性,停药后患者容易复发,使其应用及疗效均受到一定制约[4,5]。中药止血粉主要成分包括续断、没药、乳香、当归等,可用于创伤出血和术后伤口的止血,具有抗感染、止血、止痛、促进伤口愈合等多种功效[6,7]。桃仁承气汤由桃仁、桂枝、炙甘草、当归、大黄、赤芍、丹皮、芒硝等组成,具有肺肠同治,行气通瘀的功效[8,9]。桃仁承气汤对心血管系统、中枢神经系统、消化道系统等具有一定的保护作用,特别是对胃粘膜损伤具有很好的保护作用 [10-12]。本实验通过束缚 - 冷水应激法建立小鼠应激性消化道出血模型,探讨了中药止血粉联合止血后口服桃仁承气汤对上消化道出血小鼠的治疗效果及相关机制,以明确桃仁承气汤在消化道出血治疗中的应用价值。现总结报道如下。

1 资料与方法

1.1 主要研究材料

C57 野生型雄性小鼠 24 只(6-8 周龄,体重 21-25 g)购于哈尔滨兽医研究所实验动物中心 (中国农业科学院), 合格证号:009813。饲养于本研究实验动物中心,温度 23+2℃,湿度 50±5%,SPF 级环境。小鼠饲养器具、饮水、饲料具等均定期进行消毒,遵守动物实验伦理委员会制定的原则,实验过程中严禁虐待动物。中药止血粉与桃仁承气汤均有本科室保存,0.9%氯化钠购自天津大家制药有限公司生产,酶联免疫检测试剂盒购自上海生工公司,NF-κB 一抗、Caspase-3 一抗购自英国 Abcam 公司。

1.2 动物分组与处理

所有小鼠随机分为三组 - 模型组、止血组、联合组,每组 8 只小鼠,三组建立了应激性消化道出血模型。

建模后 2 周联合组给予中药止血粉联合口服桃仁承气汤治疗,止血组给予中药止血粉治疗,模型组给予等剂量的生理盐水治疗。

应激性消化道出血模型建立按参考文献[6]操作,固定小鼠四肢,垂直插入冷水中(20±1℃)6 h,水位线平齐小鼠剑突水平,1 次 /d。当小鼠全身出现僵硬少动、精神萎靡、呼吸急促、消化道隐血等症状,但是未出现激惹、乱咬装置、拼命大叫等现象表明模型制作完成。

在中药止血粉的应用中,将中药止血粉(主要成分:续断 30g、没药 20g、乳香 15g、当归 10g)碾碎后过 200 目筛,将中药粉均匀的平铺在单层纱布上, 湿润后使中药粉粘附在纱布上,然后贴敷于小鼠消化道出血部位。

在桃仁承气汤的应用中,桃仁承气汤(桃仁 10 g、桂枝 5 g、炙甘草 3 g、当归 5 g、大黄 6 g、赤芍 9 g、丹皮 4 g、芒硝 4 g)由本院中药房煎制, 小鼠灌胃用药剂量约为 0.90 g/kg/d,1 次 /d,持续 2 周。

1.3 观察指标

在治疗第 1 周与第 2 周每组各处死 4 只小鼠,然后进行下列指标的观察。(1)记录各小鼠体重,每天观察各小鼠外观形态变化、对外界反应、采食行为等。(2)在治疗第 2 周与第 4 周采集处死小鼠的静脉血 0.5 mL,3000 rpm 离心 10 min (离心半径为 15 cm),分离上层血清,检测炎症因子白介素(Interleukin,IL)-6 与 IL-8 表达水平。(3)处死小鼠后,通过精密的细尺测量溃疡的长度和宽度并进行评分,将所有分数相加即计算出单个粘膜的消化道溃疡出血指数。(4)取处死小鼠的胃上皮组织,提取总蛋白,通过 BCA 方法定量蛋白浓度并配置成所需要的蛋白浓度,放入沸水中煮 15 min 使蛋白变性。用 β-actin 作为内标,取样品 10 μg 进行 Western-Blot 分析, 添加一抗核因子 κB(nuclear fac tor kappa-B,NF-κB)、Caspase-3、β-actin, 稀释倍数均为 1:1000,4℃孵育过夜,清洗后加入二抗(1∶2000),室温孵育 1h,清洗后进行 ECL 显色, 曝光后观察目的蛋白表达情况, 利用 Image 件对各蛋白进行定量分析。

1.4 统计方法

选择 SPSS19.00 软件进行数据分析, 计量数据以均数±标准差表示,两两对比为 t 检验,三组间对比为单因素方差分析,检验水准为 α=0.05。

2 结果

2.1 小鼠体重对比

实验过程中所有小鼠都存活,止血组、联合组治疗第 2 周与第 4 周的体重高于模型组(P<0.05),联合组高于止血组(P<0.05)。见表 1。

2.2 血清炎症因子表达对比

止血组、联合组治疗第 2 周与第 4 周的血清 IL-6 与 IL-8 表达水平低于模型组(P<0.05),联合组低于止血组(P<0.05)。见表 2。

2.3 消化道溃疡出血指数对比

止血组、联合组治疗第 2 周与第 4 周的消化道溃疡出血指数对比都低于模型组(P<0.05),联合组低于止血组(P<0.05)。见表 3。

2.4 NF-κB、Caspase-3 蛋白相对表达水平对比

止血组、联合组治疗第 2 周与第 4 周的胃上皮组织 NF-κB、Caspase-3 蛋白相对表达水平低于模型组(P<0.05),联合组低于止血组(P<0.05)。见表 4。

表 1 三组治疗不同时间点的体重对比(g,$\bar{x}\pm s$)

Table 1 Comparison of body weight in three groups at different time points(g,$\bar{x}\pm s$)

Groups	n	The 2nd week	The 4th week
Model group	4	20.49±0.94	21.69±1.09
Hemostatic group	4	22.66±0.56*	24.22±0.99*
Combination Group	4	24.09±0.45*#	28.98±1.03*#
F		9.183	15.033
P		0.001	0.000

Note: compared with model group, *P<0.05; compared with hemostatic group, #P<0.05.

表 2 三组治疗不同时间点的血清炎症因子表达对比(pg/mL,$\bar{x}\pm s$)

Table 2 Comparison of Expression of Serum Inflammatory Factors in Three Groups at Different Time Points(pg/mL,$\bar{x}\pm s$)

Groups	n	IL-6		IL-8	
		The 2nd week	The 4th week	The 2nd week	The 4th week
Model group	4	44.39±3.85	46.49±3.49	32.92±2.79	35.67±3.51
Hemostatic group	4	24.59±4.59*	24.30±5.95*	23.20±4.92*	27.72±2.24*
Combination Group	4	8.98±1.69*#	8.03±1.10*#	8.09±1.91*#	6.70±2.02*#
F		21.492	45.002	18.492	12.001
P		0.000	0.000	0.000	0.000

Note: compared with model group, *P<0.05; compared with hemostatic group, #P<0.05.

表 3 三组治疗不同时间点的消化道溃疡出血指数对比($\bar{x}\pm s$)

Table 3 Comparison of bleeding index of gastrointestinal ulcer in three groups at different time points($\bar{x}\pm s$)

Groups	n	The 2nd week	The 4th week
Model group	4	18.74±2.11	19.21±1.33
Hemostatic group	4	6.73±1.03*	6.25±0.32*
Combination Group	4	1.87±0.44*#	1.55±0.24*#
F		78.193	89.111
P		0.000	0.000

Note: compared with model group, *P<0.05; compared with hemostatic group, #P<0.05.

表 4 三组治疗不同时间点的胃上皮组织 NF-κB、Caspase-3 蛋白相对表达水平对比($\bar{x}\pm s$)

Table 4 Comparison of the relative expression levels of NF-κB、Caspase-3 proteins in gastric epithelium treated by three groups at different time points($\bar{x}\pm s$)

Groups	n	NF-κB		Caspase-3	
		The 2nd week	The 4th week	The 2nd week	The 4th week
Model group	4	4.25±0.32	4.44±0.23	3.18±0.18	3.33±0.24
Hemostatic group	4	2.33±0.13*	2.18±0.18*	1.89±0.32*	1.67±0.17*
Combination Group	4	1.00±0.14*#	0.93±0.22*#	1.04±0.18*#	0.97±0.16*#
F		11.282	13.933	8.922	10.322
P		0.000	0.000	0.001	0.000

Note: compared with model group, *P<0.05; compared with hemostatic group, #P<0.05.

3 讨论

上消化道出血是消化道疾病最常见的一种,近年来该病的发病率呈显著上升趋势[13]。上消化道出血的发病诱因比较多,

主要包括幽门螺杆菌感染、吸烟、饮酒、外科手术、休克和脓毒症等[14]。应激性消化道出血为消化道出血的主要类型，其病理表现为急性浅表性胃、十二指肠黏膜糜烂和溃疡[15]。现有针对消化道出血的治疗方法仍然有限，主要为奥美拉唑、兰索拉唑、抗生素、雷尼替丁、法莫替丁，但是在实际应用中都有一定的缺陷，且伴有副作用，停药后容易复发[16,17]。

现代研究表明应激性消化道出血的发病可能与胃黏膜屏障保护功能减弱、神经内分泌失调、胃黏膜损伤因素作用相对增强密切相关[18]。中药止血粉具有补血、活血、生肌作用，可迅速止血、减轻疼痛和感染，并促进伤口愈合[19]。本研究显示实验过程中所有小鼠都存活，止血组、联合组治疗第 2 周与第 4 周的体重高于模型组(P<0.05)，联合组高于止血组(P<0.05)；止血组、联合组治疗第 2 周与第 4 周的消化道溃疡出血指数对比都低于模型组(P<0.05)，联合组低于止血组(P<0.05)，表明中药止血粉联合止血后口服桃仁承气汤能有效改善上消化道出血小鼠的症状，促进小鼠恢复体重。从机制上分析，桃仁承气汤具有行气通瘀、肺肠同治等作用，在肺损伤后胃肠功能恢复方面效果较好。其能消除肠道内氧自由基，缓解免疫功能障碍，增加肠黏膜血流量[20,21]。现代研究表明桃仁承气汤可降低机体内的器官细菌移位率，对机体肠黏膜屏障受损具有一定的保护作用[22]。

上消化道出血可对小鼠造成局部刺激，导致促肾上腺皮质激素分泌增加，而且影响物质代谢和机体的免疫系统，因此及时合理的清创止血具有重要的临床价值[23]。大量炎症因子的释放是小鼠消化道出血的重要病理特征，也是诱发消化道出血损伤和影响预后的重要因素[24]。本研究显示止血组、联合组治疗第 2 周与第 4 周的血清 IL-6 与 IL-8 表达水平低于模型组(P<0.05)，联合组低于止血组(P<0.05)，表明消化道出血小鼠会出现高炎症状态，而桃仁承气汤可以通过抗炎作用对小鼠消化道出血起到保护作用。有研究表明：桃仁承气汤可促进维持小肠黏膜上皮的完整性，增强机体的免疫功能，从而抑制炎症因子的释放，支持本研究结论[25,26]。

应激性消化道出血的发生机制之一是局部黏膜损害因素与保护因素之间的平衡失调，特别是应激性消化道出血可调控多种炎症因子的表达，进而激活 NF-κB、Caspase-3 的表达，形成瀑布效应，导致器官损伤，从而形成恶性循环[27,28]。本研究显示止血组、联合组治疗第 2 周与第 4 周的胃上皮组织 NF-κB、Caspase-3 蛋白相对表达水平低于模型组(P<0.05)，联合组低于止血组(P<0.05)。结合前人研究分析：桃仁承气汤对受损的胃肠黏膜具有较好的黏附性和止血作用，能抑制上皮细胞凋亡，抑制 NF-κB、Caspase-3 的表达，促进胃肠正常蠕动，减少肠道有害物质对细胞的损伤，从而有利于溃疡愈合[29,30]。另外，也有研究显示：桃仁承气汤可以促进内源性一氧化氮的合成和释放使胃平滑肌舒张，解除对血管的压迫，增加局部供血供氧，从而发挥保护胃黏膜的作用，与本研究结果类似[31,32]。本研究也有一定的不足，小鼠消化道出血成模过程比较长，且桃仁承气汤的给药剂量还不标准，纳入小鼠的数量比较少，可能存在研究偏倚，将在后续研究中深入分析。

总之，中药止血粉联合止血后口服桃仁承气汤在应激性消化道出血小鼠中的应用能减轻消化道组织损伤，抑制炎症因子的表达，促进小鼠正常发育，其作用机制可能与抑制 NF-κB、Caspase-3 蛋白表达有关，从而为消化道出血的临床治疗提供了实验基础。

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