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银杏达莫联合通痹胶囊治疗冠心病心绞痛的临床疗效及对血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平的影响 *

张 琴 杨 磊[△] 欧阳林旗 胡炜航 李聪杰

(湖南中医药大学第一附属医院 湖南 长沙 410000)

摘要 目的:研究银杏达莫联合通痹胶囊治疗冠心病心绞痛的临床疗效及对血清白细胞介素-1 β (IL-1 β)、肿瘤坏死因子- α (TNF- α)、内皮素-1(ET-1)、基质金属蛋白酶-9(MMP-9)水平的影响。**方法:**选取2015年8月至2016年7月我院收治的84例冠心病心绞痛患者,根据患者入院顺序分为观察组和对照组,42例每组。对照组使用通痹胶囊完成治疗,观察组在此基础上联合银杏达莫完成治疗。比较两组患者临床疗效、心绞痛发作次数、持续时间、ST段下移程度、血清IL-1 β 、TNF- α 、ET-1、MMP-9水平的变化。**结果:**治疗后,观察组临床总有效率显著高于对照组[92.86%(39/42)比66.67%(28/42)]($P<0.05$);两组患者心绞痛发作次数、持续时间、ST段下移程度、血清IL-1 β 、TNF- α 、ET-1、MMP-9水平均较治疗前显著降低($P<0.05$),且观察组以上指标均明显低于对照组($P<0.05$)。观察组和对照组的不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**银杏达莫联合通痹胶囊治疗冠心病心绞痛能有效改善患者临床症状并提高临床疗效,可能与其显著降低患者血清IL-1 β 、TNF- α 、ET-1、MMP-9水平有关。

关键词:银杏达莫;通痹胶囊;冠心病;心绞痛

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Clinical Efficacy of Ginkgo Biloba and Tongbi Capsule in Treating Angina Pectoris and Its Effects on the Serum IL-1 β , TNF- α , ET-1 and MMP-9 Levels*

ZHANG Qin, YANG Lei[△], OUYANG Lin-qi, HU Wei-hang, LI Cong-jie

(The First Affiliated Hospital of Hunan University of traditional Chinese medicine, Changsha, Hunan, 410000, China)

ABSTRACT Objective: To study the clinical efficacy of ginkgo biloba combined with Tongbi capsule in the treatment of angina pectoris and its effect on the serum interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), endothelin-1(ET-1) and matrix metalloprotein-9 (MMP-9) levels. **Methods:** From August 2015 to July 2016, 84 patients with angina pectoris in our hospital were selected and divided into the observation group and the control group according to the order of admission. The control group was treated with Tongbi Capsule, and the observation group was treated with Ginkgo biloba. The clinical efficacy, clinical symptoms, serum IL-1 β , TNF- α , ET-1 and MMP-9 levels were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group [92.86% (39/42) vs 66.67% (28/42)] ($P<0.05$). The times of angina pectoris, duration and ST segment depression showed no difference between two groups before treatment ($P>0.05$). After treatment, the number of episodes and duration and ST segment depression were significantly lower than those before treatment in the two groups ($P<0.05$). Compared with the control group, the number of angina pectoris, duration, ST segment depression were lower ($P<0.05$). There was no significant difference in the serum IL-1 β , TNF- α , ET-1 and MMP-9 levels between the two groups before treatment ($P>0.05$). After treatment, IL-1 β , TNF- α , ET-1, MMP-9 were lower than before treatment ($P<0.05$). Compared with the control group, the levels of IL-1 β , TNF- α , ET-1 and MMP-9 in the observation group were lower after treatment($P<0.05$). There was no significant difference in the incidence of adverse reaction between two groups($P>0.05$). **Conclusion:** Ginkgo biloba and Tongbi Capsule could effectively improve the serum levels of IL-1 β , TNF- α , ET-1 and MMP-9 of patients with angina pectoris and improve the clinical symptoms.

Key words: Ginkgo biloba; Tongbi capsule; Coronary heart disease; Angina pectoris

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前言

冠心病心绞痛属于较为常见的一种心血管疾病,若不能有效控制此疾病极有可能导致心源性猝死、急性心肌梗死等严重

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作者简介:张琴(1981-),硕士研究生,主管药师,研究方向:中药制剂及中药药理学,E-mail: dboyzq1@163.com

[△] 通讯作者:杨磊(1978-),博士,副主任药师,研究方向:中药炮制及有效物质基础研究,E-mail: yanglei30@sohu.com

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心血管事件,给患者生命安全带来严重威胁^[1]。当前临床治疗冠心病心绞痛较为常见的方式为药物治疗。由于冠心病心绞痛患者伴有较为复杂的心绞痛,并且发病人群以老年人为主,此类患者极易合并其他慢性病,因此临床中在用药方面有众多选择方式^[2]。临床中在用药方面可依据患者的有关临床指标及个体情况作出相应调整。在传统医学看来,冠心病心绞痛作为“心痛”、“胸痹”等范畴,本虚标实作为此病的主要病机,大多数患者因为年老体虚、壅堵心脉、运血无力、气血生化匮乏,再加之寒邪侵心、易形成痰浊、寒凝、气滞、血瘀等^[3]。相关研究者提出在延缓或防治冠心病心绞痛进程方面使用中药治疗能发挥重要作用^[4]。为给临床在治疗冠心病心绞痛方面提供更多可借鉴之处,本研究主要探讨了银杏达莫联合通痹胶囊治疗冠心病心绞痛进行研究及对血清白细胞介素-1 β (Interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、内皮素-1 (endothelin-1, ET-1)、基质金属蛋白酶-9 (matrix metalloprotein-9, MMP-9) 水平的影响。

1 资料与方法

1.1 临床资料

选取 2015 年 8 月至 2016 年 7 月在我院进行治疗的冠心病心绞痛患者 84 例,纳入标准:① 患者的临床诊断和《不稳定型心绞痛诊断和治疗建议》^[5]中的有关标准相符;② 心肌梗死标志物检测正常;③ 对本次研究中所使用的药物无过敏史。排除标准:① 肝肾功能严重障碍者;② 心肌炎、心律失常、心肌梗死、心力衰竭等其他心脏有关的疾病;③ 肾炎、肺炎等其他感染性疾病。本次研究已取得我院伦理委员会批准,及得到患者及家属同意。

根据患者入院顺序划分为观察组和对照组,42 例每组。观察组中,男性 26 例,女性 16 例;年龄为 57~76 岁,平均(67.98 $\pm$ 2.32)岁;病程为 3~35 个月,平均(18.98 $\pm$ 3.51)个月;基础疾病:高血压 14 例,高血脂 18 例,糖尿病 21 例。对照组中,男性 23 例,女性 19 例;年龄为 58~78 岁,平均(68.01 $\pm$ 2.31)岁;病程为 4~37 个月,平均(19.01 $\pm$ 3.57)个月;基础疾病:12 例高血压,17 例高血脂,19 例糖尿病。两组患者性别、年龄等方面比较无显著差异($P>0.05$),具有可比性。

1.2 治疗方法

患者入院后均采取抗血小板聚集、抗凝、硝酸酯类、钙拮抗剂、血管紧张素转换酶抑制剂、 β -受体阻滞剂等常规治疗。对照组在常规治疗基础上结合通痹胶囊(生产厂家:烟台渤海制药集团有限公司)完成治疗,0.3 g/粒,3 粒/次,3 次/天。观察组在对照组治疗基础上加以 20 mL 的银杏达莫注射液(生产厂家:贵州益佰制药股份有限公司)完成治疗,和 250 mL 的 5%葡萄糖混合后,行静脉滴注的方式给药,1 次/天。所有患者均需连续治疗 2 个月。

1.3 观察指标

1.3.1 临床疗效评价 评价标准如下:治疗后,心绞痛症状消失则为显效;经治疗后,心绞痛的疼痛时间或发作次数减少,程度有所缓解则为有效;经治疗,临床症状无变化甚至心绞痛发作时间增加、发作次数也增加则为无效^[5]。

1.3.2 临床症状 比较两组患者治疗前后心绞痛发作频次、持续时间、S 段下移程度,根据所有 ST 段下移次数中最为严重的视为本次评估值。

1.3.3 血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平分析 两组患者在治疗前后抽取空腹静脉血 5 mL,转速 3000 r/min,离心 10 min,血清分离后,提取上清液,使用酶联免疫吸附法检测 IL-1 β 、TNF- α 、MMP-9,人 TNF- α 检测试剂盒和人 IL-1 β 检测试剂盒由上海基免生物技术有限公司提供,由美国 R&D 公司提供 MMP-9 试剂盒。使用放射免疫法检测 ET-1 水平,ET 放射免疫试剂盒来自南京建成生物技术公司,均根据说明书严格操作。

1.4 统计学处理

选取 SPSS11.5 软件包对本次实验数据予以处理,用($\bar{x} \pm s$)对计量资料进行表示,进行 t 检验,用[n(%)]对计数资料进行表示,予以 χ^2 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者临床疗效比较

治疗后,观察组临床总有效率显著高于对照组[92.86% (39/42)比 66.67%(28/42)]($P<0.05$),见表 1。

表 1 两组患者临床疗效评价[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Cases	Effective	Valid	Invalid	Total effective
Observation	42	30(71.43)	9(21.43)	3(7.14)	39(92.86)*
Control	42	11(26.19)	17(40.48)	14(33.33)	28(66.67)

Note: Compared with control group, * $P<0.05$.

2.2 两组患者临床症状比较

治疗前,两组患者心绞痛发作次数、持续时间、ST 段下移程度比较差异无统计学意义($P>0.05$);治疗后,两组患者心绞痛发作次数、持续时间、ST 段下移程度较治疗前显著降低($P<0.05$),和对照组相比,观察组的心绞痛发作次数、持续时间、ST 段下移程度较低($P<0.05$),见表 2。

2.3 两组治疗前后血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平比较

治疗前,两组患者血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平

比较差异无统计学意义($P>0.05$),治疗后,两组患者血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平较治疗前显著降低($P<0.05$),和对照组相比,观察组的血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平较低($P<0.05$),见表 3。

3 讨论

冠心病心绞痛主要是因为血液动力学基于冠状动脉粥样硬化之上而发生的变化,心肌短暂缺氧、缺血而出现的心前区疼

痛,可能会牵涉左肩背、咽喉、牙齿等部位,以至于发生疼痛不适之感,也是心血管不良事件最为主要的预警信号,发作频繁且不加以系统治疗,其预后较差^[6,7]。当前,临床上在治疗此病主要有解除冠脉痉挛、降低心肌耗氧量、抗凝、抗血小板聚集、扩

张血管等方式^[8,9]。在治疗冠心病心绞痛中,尽管采取西医治疗能获得较好的临床疗效,然而伴随着用药疗程的增加,其毒副作用也会越来越明显,长时间使用此药物,药物依赖性较高^[10,11]。

表 2 两组患者临床症状分析($\bar{x} \pm s$)Table 2 Analysis of the clinical symptom between two groups($\bar{x} \pm s$)

Items	Observation(n=42)		Control(n=42)	
	Before treatment	After treatment	Before treatment	After treatment
Frequency of episodes (time/week)	15.24 $\pm$ 1.87	7.24 $\pm$ 0.78 ^{*#}	15.28 $\pm$ 1.91	12.38 $\pm$ 1.04 [*]
Duration(min/time)	8.76 $\pm$ 0.98	3.12 $\pm$ 0.32 ^{*#}	8.81 $\pm$ 0.97	6.76 $\pm$ 0.65 [*]
ST segment down level(mm)	1.71 $\pm$ 0.21	0.87 $\pm$ 0.09 ^{*#}	1.73 $\pm$ 0.23	1.24 $\pm$ 0.12 [*]

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

表 3 两组治疗前后血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平比较($\bar{x} \pm s$)Table 3 Comparison of the serum IL-1 β , TNF- α , ET-1, MMP-9 levels before and after treatment between two groups($\bar{x} \pm s$)

Items	Observation(n=42)		Control(n=42)	
	Before treatment	After treatment	Before treatment	After treatment
IL-1 β (ng/L)	6.93 $\pm$ 0.63	5.33 $\pm$ 0.56 ^{*#}	6.97 $\pm$ 0.62	4.21 $\pm$ 0.41 [*]
TNF- α (ng/L)	50.12 $\pm$ 5.87	28.32 $\pm$ 3.14 ^{*#}	50.14 $\pm$ 5.92	38.43 $\pm$ 4.01 [*]
ET-1(ng/L)	114.87 $\pm$ 12.02	69.32 $\pm$ 5.31 ^{*#}	115.03 $\pm$ 11.98	85.98 $\pm$ 7.94 [*]
MMP-9(ug/L)	187.43 $\pm$ 14.54	94.21 $\pm$ 9.87 ^{*#}	187.07 $\pm$ 15.01	135.09 $\pm$ 12.44 [*]

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

中医药治疗作为治疗冠心病心绞痛时重要的组成部分,借助"整体观念、辨证论治"方式,具有西医治疗难以代替的作用,主要有整体调整、高效低毒等优点^[12-14]。由于此病具有久病必虚、病程长等特点,治疗冠心病心绞痛的基本原则是活血,益气散寒祛瘀化浊为辅助方案,活血化瘀、益气培元属于较为重要的治疗方案^[15,16]。通痹胶囊属于中药复方制剂中的一种,具备消肿止痛、活血通络、祛风胜湿、调补气血的功能^[17,18]。通痹胶囊中的白花蛇舌草、穿山甲、地龙、全蝎等血肉之品可通经活络、荡涤痰浊、祛邪散瘀,在痰湿瘀滞、邪气深入、痹痛日久者中具有气血冲合、浊去凝开的功能;川乌、没药、乳香、草乌、能活血止痛;当归能调经止痛、补血和血;红花、桃仁、丹皮等具有活血化瘀止痛的功能;路路通、木瓜、牛膝等中药可通利血脉;马钱子能通络止痛、祛风胜湿,具有开通经络的功能;加以天麻能镇静镇痛和息风止痉^[19,21]。在上述诸多药物联合使用下,在冠心病心绞痛患者中能发挥脉络通畅、血瘀消除、心气得补的功能,并且可自行消除胸痹心痛。

银杏达莫作为银杏叶提取物和双嘧达莫定的复方制剂,在血栓形成中能发挥较好的抑制功能,能扩张血管、改善心肌供血、抗血小板凝聚^[22,23]。银杏叶提取物作为黄酮苷类物质,在药理试验研究中得出此药物对血小板细胞膜上的 PAF 受体能发挥竞争性拮抗功能,能抵抗血小板凝聚,以至于避免血栓的形成,降低血液粘度^[24-26]。除此之外,银杏叶提取物能间接性的抗脂质过氧化,能清除自由基,有利于细胞功能和结构完整性的维持,能扩张冠状动脉,减少心肌耗氧量及改善心肌缺氧缺血状态^[27]。双嘧达莫定在银杏总黄酮对血小板抗凝聚的作用

中具有加强的功能,为此此药物能有效改善冠心病心绞痛患者的临床疗效。本次研究结果显示:通过对冠心病心绞痛患者予以银杏达莫联合通痹胶囊治疗后,发现心绞痛发作次数、持续时间、ST 段下移程度显著少于单纯通痹胶囊治疗者,且临床有效率显著高于单纯通痹胶囊治疗者。

研究表明炎症反应在冠心病心绞痛的发生发展中起着极其重要的作用。TNF- α 可调节免疫反应,对冠状动脉上皮平滑肌细胞增殖具有诱导的作用,并且会诱导 IL- β 等炎症因子的产生,促进动脉粥样硬化的发生^[28]。IL- β 同时作为血清炎症指标的一类,对血管功能具有调节的作用,在冠心病心绞痛患者的水平较高。ET-1、MMP-9 水平会对动脉粥样硬化斑块稳定性造成严重影响,血管内皮功能正常能抑制血小板聚集、调节血管张力、阻碍炎症反应、有利于血浆纤溶活性的改善及平滑肌增殖等能得到有效调节,动脉粥样硬化的最主要的因素是因为血管内皮功能受损,已有研究者提出在冠心病心绞痛患者中伴有严重的血管内皮功能受损^[29]。本次研究结果显示银杏达莫联合通痹胶囊治疗的冠心病心绞痛患者血清 IL- β 、TNF- α 、ET-1、MMP-9 水平显著降低,且降低的效果显著优于单纯通痹胶囊治疗者,提示两者药物联合使用能有效降低患者血清 IL- β 、TNF- α 、ET-1、MMP-9 水平有效减轻炎症反应,进而阻碍平滑肌细胞和内皮细胞的增生,降低血管紧张素 II 受体表达几 MMPs 的产生,对血管内皮功能发挥着明显的保护作用。

综上所述,银杏达莫联合通痹胶囊治疗冠心病心绞痛能有效改善患者临床症状并提高临床疗效,可能与其明显降低患者血清 IL-1 β 、TNF- α 、ET-1、MMP-9 水平有关。

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