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美托洛尔联合丹红注射液对老年慢性心力衰竭患者血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平的影响*

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摘要 目的: 研究美托洛尔联合丹红注射液对老年慢性心力衰竭患者血清生长分化因子-15 (Growth differentiation factor-15, GDF-15)、前体 N 末端前脑利钠肽 (Pro N-terminal pro brain natriuretic peptide, NT-pro BNP)、细胞黏附分子-1 (Cell adhesion molecule-1, ICAM-1)、 β 内啡肽 (Beta endorphin, β -EP) 水平的影响。**方法:** 选择 2015 年 10 月~2019 年 9 月我院收治的 328 例老年慢性心力衰竭患者, 随机分为两组。对照组口服美托洛尔, 初始剂量为每次 6.25 mg, 每天 2 次, 慢慢增加至每次 12.5 mg, 每天 2 次; 观察组在美托洛尔的基础上, 静脉滴注丹红注射液, 每次 20 mL, 每天 1 次。均治疗 1 个月。**结果:** 观察组的有效率明显高于对照组 ($P<0.05$); 治疗后, 两组的左心室舒张期末内径 (End diastolic diameter of left ventricle, LVEDD)、6 min 步行试验 (6MWT)、左心室射血分数 (Left ventricular ejection fraction, LVEF)、左心室收缩期末内径 (Left ventricular end systolic diameter, LVESD) 均明显改善, 且观察组的 LVEDD、6MWT、LVEF、LVESD 明显优于对照组 ($P<0.05$); 治疗后, 两组的血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平明显降低 ($P<0.05$), 且观察组的血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平明显低于对照组 ($P<0.05$)。**结论:** 美托洛尔联合丹红注射液对老年慢性心力衰竭具有显著的疗效, 其机制可能与降低血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平有关。

关键词: 美托洛尔; 丹红注射液; 慢性心力衰竭; 生长分化因子-15; 前体 N 末端前脑利钠肽; 细胞黏附分子-1; β 内啡肽

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Effects of Metoprolol Combined with Danhong Injection on the Levels of Serum GDF-15, NT proBNP, ICAM-1 and β -EP in Elderly Patients with Chronic Heart Failure*

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ABSTRACT Objective: To study the effects of metoprolol combined with Danhong Injection on serum growth differentiation factor-15 (GDF-15), pro N-terminal pro brain natriuretic peptide (NT Pro BNP), cell adhesion molecule-1 (ICAM-1), beta endorphin (β -EP) in elderly patients with chronic heart failure. **Methods:** Selected 328 cases of elderly patients with chronic heart failure who were treated in our hospital from October 2015 to September 2019, divided into two groups randomly. In the control group, metoprolol was taken orally, the initial dose was 6.25 mg per time, twice a day, slowly increased to 12.5 mg per time, twice a day. In the observation group, on the basis of metoprolol, Danhong injection was infused intravenously, 20 mL each time, once a day. All patients were treated for one month. **Results:** The effective rate of the observation group was significantly higher than control group ($P<0.05$). After treatment, the LVEDd, 6MWT, LVEF and LVESD of the two groups were significantly improved, and the LVEDd, 6MWT, LVEF and LVESD of the observation group were significantly better than those of the control group ($P<0.05$). After treatment, the levels of serum GDF-15, NT proBNP, ICAM-1 and β -EP in the two groups decreased significantly ($P<0.05$), the levels of GDF-15, NT proBNP, ICAM-1 and β -EP in the observation group were significantly lower than those in the control group ($P<0.05$). **Conclusion:** Metoprolol combined with Danhong injection has a significant effect on chronic heart failure in the elderly. The mechanism may be related to the decrease of serum GDF-15, NT proBNP, ICAM-1 and β -EP levels.

Key words: Metoprolol; Danhong Injection; Chronic Heart Failure; Growth Differentiation Factor-15; Precursor N-Terminal Pro Brain Natriuretic Peptide; Cell Adhesion Molecule-1; β Endorphin

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前言

心力衰竭是因为心肌病、心肌梗死、炎症反应和血流动力学的负荷过重等任何因素导致的心肌受损,使得心肌的功能及结构出现改变,造成心室的泵血功能或者充盈功能明显降低,主要表现为呼吸困难、体液潴留以及乏力等^[1]。慢性心力衰竭则指的是患者的心力衰竭状态持续存在。慢性心力衰竭是大部分心血管疾病患者最终的归属,也是最主要的一个死亡原因,是临床常见的综合征^[2-4]。由于老年慢性心力衰竭患者的基础病多,病因较为复杂,且对药物的耐受性较差,故病死率比较高,必须对其心功能进行调节,以达到理想的预后效果^[5-7]。目前针对该病的主要治疗原则为扩张血管,去除病因,利尿以降低心脏负荷,强心以促进心排血量的增加^[8]。常规的抗心力衰竭药物虽然能在一定程度改善预后,但致残率及病死率较高。美托洛尔能阻断交感神经的过度激活,改善心肌纤维化,减少儿茶酚胺释放,减少耗氧量,降低血压以及心率,提高左室功能^[9]。丹红注射液具有扩张冠状动脉、活血化瘀、抑制血小板聚集、改善血液流速的作用。目前尚未见将二者联用的报道。本研究创新性地将美托洛尔与丹红注射液联用,并分析其对老年慢性心力衰竭患者血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平的影响。

1 资料与方法

1.1 一般资料

选择 2015 年 10 月~2019 年 9 月我院收治的 328 例老年慢性心力衰竭患者,纳入标准:均符合相关的诊断标准^[10],心功能均为 II~IV 级,年龄 60~85 岁,均知情同意。排除标准:(1)伴有房室传导阻滞、急性心肌梗死和支气管哮喘预激综合征的患者;(2)伴有肥厚性心肌病、心脏瓣膜病不稳定心绞痛、活动性心肌炎和风湿性心脏病的患者;(3)有严重肝肾功能不全者;(4)伴有凝血功能异常和自身免疫系统疾病的患者;(5)伴有恶性肿瘤和严重感染的患者;(6)对美托洛尔和丹红注射液过敏的患者;(7)植入起搏器的患者。用抽签法随机分为两组。观察组 164 例,男 90 例,女 74 例;年龄 60~85 岁,平均(64.17 $\pm$ 2.89)岁;病程 2.1~12.3 年,平均(6.33 $\pm$ 1.04)年;基础疾病:肥厚型非梗阻性心肌病 3 例,冠心病 135 例,风湿性心脏病 11 例,先天性心脏病 10 例,扩张性心肌病 5 例;NYHA 心功能分级:II 级

患者 59 例,III 级患者 81 例,IV 级患者 24 例。对照组 164 例,男 89 例,女 75 例;年龄 60~85 岁,平均(64.69 $\pm$ 2.54)岁;病程 2.1~12.3 年,平均(6.48 $\pm$ 0.93)年;基础疾病:肥厚型非梗阻性心肌病 3 例,冠心病 134 例,风湿性心脏病 11 例,先天性心脏病 10 例,扩张性心肌病 6 例;NYHA 心功能分级:II 级患者 59 例,III 级患者 82 例,IV 级患者 23 例。两组的基线资料具有可比性($P>0.05$)。

1.2 治疗方法

两组均进行抗血小板聚集、强心、营养心肌和降血脂等常规治疗。对照组:口服美托洛尔(国药准字 H32025391,阿斯利康制药公司,25 mg/片),初始剂量为每次 6.25 mg,每天 2 次,慢慢增加至每次 12.5 mg,每天 2 次。观察组:在美托洛尔的基础上,静脉滴注丹红注射液(国药准字 Z20026866,山东丹红制药有限公司,10 mL/支),每次 20 mL,每天 1 次。两组均治疗 1 个月。

1.3 观察指标

疗效标准^[11]:① 显效:慢性心力衰竭患者的症状明显改善,心律失常基本消失或者减少幅度大于 90%,心功能分级提高超过 2 级;② 有效:慢性心力衰竭患者的症状有所改善,心律失常基本消失或者减少幅度大于 50%,心功能分级提高超过 1 级;③ 无效:慢性心力衰竭患者的症状出现恶化或无任何改变,心律失常和心功能分级没有无显著的改变。

治疗前后,用彩色多普勒超声检查患者的 LVEDD、6MWT、LVEF 以及 LVESD。

治疗前后,空腹采集 3 mL 上肢静脉血,采取放射免疫法检测血清 β -EP 水平,采取电化学发光免疫法检测 NT-pro BNP 水平,采取 ELISA 检测 GDF-15 和 ICAM-1 水平,试剂盒均购自国药集团化学试剂有限公司。

1.4 统计学分析

采用 SPSS 21.0,两组间计量资料对比用 t 检验,计数资料用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组临床疗效对比

观察组的总有效率明显高于对照组(92.68% vs. 74.39%, $P<0.05$),见表 1。

表 1 两组临床疗效比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	The total effect rate
Control group	164	51(31.10)	71(43.29)	42(25.61)	122(74.39)
Observation group	164	70(42.68)	82(50.00)	12(7.32)	152(92.68)*

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

2.2 两组心功能对比

治疗后,两组的 LVEDD、6MWT、LVEF、LVESD 均明显改善,且观察组的 LVEDD、6MWT、LVEF、LVESD 明显优于对照组($P<0.05$),见表 2。

2.3 两组血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平对比

治疗后,两组的血清 GDF-15、NT-proBNP、ICAM-1、 β -EP

水平明显降低($P<0.05$),且观察组的血清 GDF-15、NT-proBNP、ICAM-1、 β -EP 水平明显低于对照组($P<0.05$),见表 3。

2.4 不良反应

治疗过程中,两组均未发生头晕、心动过速、水肿、皮疹和胃肠不适等药物相关不良反应。

表 2 两组治疗前后的心功能对比($\bar{x} \pm s$)

Table 2 Comparison of cardiac function between the two groups before and after treatment ($\bar{x} \pm s$)

Groups	n		LVEDD (mm)	6MWT (m)	LVEF (%)	LVESD (mm)
Control group	164	Before treatment	51.27± 12.46	405.74± 129.78	36.53± 6.74	46.37± 11.26
		After treatment	40.38± 9.25 [#]	520.29± 134.41 [#]	49.16± 7.29 [#]	35.45± 7.63 [#]
Observation group	164	Before treatment	51.43± 11.67	406.38± 124.52	36.53± 6.28	47.14± 10.38
		After treatment	45.38± 8.43 [#]	463.72± 129.63 [#]	42.69± 8.41 [#]	40.27± 9.34 [#]

Note: Compared with the control group, ^{*}*P*<0.05; compared with before treatment, [#]*P*<0.05.

表 3 两组治疗前后的血清 GDF-15、NT-proBNP、ICAM-1、β-EP 水平对比($\bar{x} \pm s$)

Table 3 Comparison of serum GDF-15, NT proBNP, ICAM-1 and β - EP levels between the two groups before and after treatment ($\bar{x} \pm s$)

Groups	n		GDF-15 (ng·L ⁻¹)	NT-pro BNP(ng·L ⁻¹)	ICAM-1 (ng·L ⁻¹)	β-EP (ng·L ⁻¹)
Control group	164	Before treatment	973.24± 45.19	792.86± 34.85	61.32± 11.49	86.29± 13.47
		After treatment	391.52± 34.85 [#]	384.26± 22.57 [#]	44.86± 10.29 [#]	53.64± 10.89 [#]
Observation group	164	Before treatment	974.65± 48.67	794.36± 35.27	60.85± 10.73	85.43± 12.71
		After treatment	237.44± 19.62 [#]	271.63± 20.14 [#]	35.71± 9.36 [#]	42.17± 10.63 [#]

Note: Compared with the control group, ^{*}*P*<0.05; compared with before treatment, [#]*P*<0.05.

3 讨论

慢性心力衰竭大多由相关的心脏疾病发展而成,主要的发病群体为老年人,表现出乏力、呼吸困难等症状,病死率极高^[11,12]。该病是因受到各种因素的影响造成机体的心肌舒缩功能出现障碍,心脏的排血量降低,继而引发血流动力学障碍,心肌肥厚,心脏结构改变,心室重构,最后造成心室泵血功能降低^[5,6]。患者由于心肌收缩会出现不同严重程度的乏力,常常会产生呼吸困难以及疲惫等表现,对其躯体功能和心理健康产生了非常严重的影响^[13-16]。临床上主要采取血管扩张剂及强心药进行治疗,虽能获得一定的疗效,但无法阻止疾病的进展,仍具有较高的死亡率^[17]。因此,需要寻找积极有效的疗法。

美托洛尔主要对患者机体中交感神经导致的血管收缩发挥抑制效果,可以降低外周循环的阻力,使心脏的后负荷明显降低,并且减慢心率,造成心肌的张力下降,从而造成患者机体的心肌耗氧量明显降低,并且血液的黏度降低,从而改善心室的舒张功能^[18-20]。丹红注射液的成分主要包括丹参酮、丹酚酸、红花等,具有活血化瘀和通脉舒络的功效。现代药理学研究发现,其能改善微循环,使冠状动脉得到扩张,抑制微血栓的进一步形成,减少血液的黏稠度,促使纤维蛋白原出现溶解,改善心肌的供血供氧,加快血流速度,预防动脉粥样硬化等^[21]。丹参的有效成分丹参酮和丹参素都能明显对抗血小板的聚集,明显减少血浆血栓素 A 含量,丹参酮 II A 能抑制低密度脂蛋白导致的血管内皮受损,有效保护血管内皮。红花能抑制血小板的聚集,增加冠脉的血流量,显著增加纤维蛋白的溶解活性,进而使血栓溶解,且抑制血栓的形成^[22]。红花的有效成分是红花黄素,其可以增加红细胞的变形性,减少血液的黏稠度,减轻血管外周的阻力,改善心肌的供血,增加冠脉的血流量,增加纤维蛋白的溶解,抑制血栓的形成^[23]。因此,本研究对老年慢性心力衰竭患者采用美托洛尔联合丹红注射液进行治疗,取得了满意的效果。

GDF-15 属于转化生长因子-β(TGF-β)超家族的成员,具

有促进细胞凋亡、抑制细胞生长和调节炎症反应等效果^[24,25]。NT-pro BNP 作为一种心脏神经激素,主要合成于机体的心室,正常人体血中的 NT-pro BNP 水平较低,主要用于指导心衰治疗、评价心功能以及评估心衰的预后等^[26,27]。ICAM-1 能促进内皮细胞和炎症细胞之间的黏附作用,从而使炎症反应加重,还能增加内皮细胞和血小板之间的黏附作用,使血栓的风险升高,加重心肌缺血情况^[28,29]。β-EP 可以有效评估心力衰竭患者的心肌受损程度以及血管内皮功能^[30]。本研究发现,观察组的血清 GDF-15、NT-proBNP、ICAM-1、β-EP 水平明显低于对照组。表明丹红注射液联合美托洛尔能有效改善心力衰竭患者的血管内皮功能,从而促进心功能的改善。

综上所述,美托洛尔联合丹红注射液对老年慢性心力衰竭具有显著的疗效,其机制可能与降低血清 GDF-15、NT-proBNP、ICAM-1、β-EP 水平有关。

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