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左西孟旦联合螺内酯对慢性心力衰竭患者血清炎症因子水平及心室重构的影响研究 *

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摘要 目的:研究左西孟旦联合螺内酯对慢性心力衰竭患者血清炎症因子水平及心室重构的影响。**方法:**选择 2015 年 1 月 -2017 年 12 月我院干部病房收治的 88 例慢性心力衰竭患者,将其随机分为两组。对照组单纯口服螺内酯,每次 20 mg,每天 1 次;观察组联合采取左西孟旦治疗。观察和比较两组治疗前后的心功能指标(左心室舒张期末内径、6 min 步行试验、左心室射血分数以及左心室收缩期末内径),血清肿瘤坏死因子 -α(tumor necrosis factor-α,TNF-α)、白介素 -6 (interleukin-6,IL-6)、高敏 C- 反应蛋白(high sensitivity C-reactive protein,hs-CRP)、N 端脑钠肽前体(N-terminal pro-brain natriuretic peptide,NT-proBNP)水平的变化情况。**结果:**治疗后,观察组的有效率明显高于对照组(90.91% vs. 72.73%,*P<0.05*);两组治疗后左心室舒张期末内径、左心室收缩期末内径、血清 hs-CRP、TNF-α、IL-6 和 NT-proBNP 水平均较治疗前显著降低,而左心室射血分数及 6 min 步行试验均较治疗前明显增加(*P<0.05*),且观察组左心室舒张期末内径、左心室收缩期末内径、血清 hs-CRP、TNF-α、IL-6 和 NT-proBNP 水平明显低于对照组,左心室射血分数及 6 min 步行试验显著高于对照组(*P<0.05*)。**结论:**左西孟旦联合螺内酯治疗慢性心力衰竭患者可能显著提高其临床疗效,可能与其有效改善患者的心功能以及心室重构、减轻机体炎症反应有关。

关键词:左西孟旦;螺内酯;慢性心力衰竭;炎症因子;心室重构

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Effects of Levosimendan Combined Spironolactone on the Serum Inflammatory Factors Levels and Ventricular Remodeling in Patients with Chronic Heart Failure*

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ABSTRACT Objective: To study the effect of levosimendan combined spironolactone on the serum inflammatory factors levels and ventricular remodeling in patients with chronic heart failure. **Methods:** 88 cases of patients with chronic heart failure who were treated in our hospital from January 2015 to December 2017 were selected and randomly divided into two groups. The control group was treated with spironolactone alone, while the observation group was treated with levosimendan. The cardiac function indexes (left ventricular end-diastolic diameter, 6-minute walking test, left ventricular ejection fraction and left ventricular end-systolic diameter), serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), high sensitivity C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were observed and compared between the two groups before and after treatment. **Results:** After treatment, the effective rate of observation group was significantly higher than that of the control group (90.91% vs. 72.73%, *P<0.05*). After treatment, left ventricular end diastolic diameter, left ventricular end systolic diameter, serum hs-CRP, TNF-α, IL-6 and NT-proBNP levels were significantly lower than those before treatment, while the left ventricular ejection fraction and 6-minute walking test were significantly increased (*P<0.05*), and the left ventricular end diastolic diameter, left ventricular end systolic diameter, serum levels of hs-CRP, TNF-α, IL-6 and NT-proBNP were significantly lower than those in the control group. The left ventricular ejection fraction and 6-minute walking test were significantly higher than those in the control group (*P<0.05*). **Conclusion:** Levosimendan combined with spironolactone may significantly improve its clinical efficacy in the treatment of chronic heart failure, which may be related to the effective improvement of cardiac function, ventricular remodeling and alleviating inflammation.

Key words: Levosimendan; Spironolactone; Chronic heart failure; Inflammatory factors; Ventricular remodeling

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前言

慢性心力衰竭为不同心脏疾病的最终结果，是一种以运动能力降低以及劳力性呼吸困难为特点的临床综合征[1,2]。慢性心力衰竭的发病机制比较复杂，主要与心室重塑、心肌缺血、肾素 - 血管紧张素 - 醛固酮系统以及交感神经系统的过度激活相关[3-5]。患者的临床表现为运动耐力下降、液体潴留(腹部或者腿部水肿)以及呼吸困难。患者一旦出现慢性心力衰竭，就有可能发生窒息感或呼吸困难，甚至因治疗不及时引发呼吸衰竭导致死亡。

慢性心力衰竭的治疗常采用利尿剂减轻心脏负荷，螺内酯为较为常用药物。螺内酯可以通过与醛固酮(aldosterone，ALD)受体相结合，促进排尿，有助于降低慢性心力衰竭患者的病死率，还可以显著改善血管内皮功能，促进内皮一氧化碳的合成，从而扩张血管、降低血压和促进血液流通[6-8]。近年来，左西孟旦越来越多运用于心衰治疗，尤其在传统治疗疗效不佳时，但临床上尚未见左西孟旦联合螺内酯治疗慢性心力衰竭患者的相关研究报道。因此，本研究将两种药物联合使用，主要探讨其对慢性心力衰竭患者炎症因子及心室重构的影响，以明确其临床应用价值。

1 资料与方法

1.1 一般资料

选择 2015 年 1 月～2017 年 12 月我院干部病房收治的 88 例慢性心力衰竭患者，均符合《慢性心力衰竭临床诊断标准》，经 X 线、心电图或冠脉造影确诊，无恶性肿瘤，无左西孟旦以及螺内酯药物禁忌，且排除严重的感染、肾、肝功能不全患者，急性冠状动脉综合征患者，合并自身免疫系统疾病、内分泌疾病的患者，器质性心脏瓣膜病、限制型、肥厚型心肌病患者，近半年来受到创伤或伴外科手术患者，所有患者均签署知情同意书。将患者随机分为两组：观察组 44 例，男 24 例，女 20 例；年龄 40 ~ 83 岁，平均(58.73 ± 12.46)岁；病程 2~ 18 年，平均(10.62 ± 1.42) 年；心功能分级：Ⅱ级 13 例，Ⅲ级 24 例，Ⅳ级 7 例；高血压性心脏病 19 例，冠心病 15 例，风湿性心脏病 2 例，瓣膜性心脏病 8 例。对照组 44 例，男 25 例，女 19 例；年龄 41 ~ 82 岁，平均(59.63 ± 13.29)岁；病程 2 ~ 18 年，平均(10.47 ± 1.82)年；心功能分级：Ⅱ级 12 例，Ⅲ级 25 例，Ⅳ级 7 例；高血压性心脏病 20 例，冠心病 15 例，风湿性心脏病 2 例，瓣膜性心脏病 7 例。两组的基线资料比较差异均无统计学意义(*P>0.05*)，具有可比性。

1.2 治疗方法

两组均采用氧疗、调整血糖和血压，控制钠盐的摄取量，口服单硝酸异山梨酯缓释片扩张血管，口服地高辛片强心，口服呋塞米片利尿等常规治疗。对照组单纯口服螺内酯，每次 20 mg，每天 1 次，共给药 8 w。观察组联合采取左西孟旦注射液 12 μg/kg 治疗，静脉滴注 10 min 后，按照 0.1 μg/ kg/min 的剂量持续微量泵入 1 h，然后按照 0.2 μg/kg/min 的剂量持续微量泵入 23 h，1 w 后再采取左西孟旦治疗 1 次，总共治疗 2 次。

1.3 观察指标

比较两组的临床治疗有效率：① 显效：患者的症状明显改善，心功能分级提高超过 2 级；② 有效：患者的症状有所改善，心功能分级提高超过 1 级；③ 无效：患者的症状出现恶化或无任何改变，心功能分级无显著的改变。

观察两组治疗前后的心功能指标变化情况(左心室舒张期末内径、6 min 步行试验、左心室射血分数以及左心室收缩期末内径)。

观察两组肿瘤坏死因子(TNF)-α、白介素(IL)-6 以及高敏 C- 反应蛋白(hs-CRP)的改变情况，其中，血清 hs-CRP 水平采用免疫比浊法检测，血清 TNF-α 和 IL-6 水平采用 ELISA 双抗体夹心法检测，试剂盒均购自上海邦奕生物科技有限公司。NT-proBNP 水平采用电化学发光 - 夹心免疫分析法检测，试剂盒购自上海邦奕生物科技有限公司。

1.4 统计学分析

实验数据采用 SPSS19.0 软件进行统计学分析，计量资料以 $\bar{x}\pm s$ 表示，组间和组内对比用 t 检验，组间率的比较用 x^2 检验，以 *P<0.05* 表明差异有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后，与对照组[72.73%(32/44)]比较，观察组总有效率[90.91%(40/44)]显著升高，差异具有统计学意义(*P<0.05*)。

表 1 两组临床疗效比较[例(%)]

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

Group	n	Effective	Valid	Invalid	The total effect rate
Observation group	44	19 (43.18)	21 (47.73)	4 (9.09)	90.91*
Control group	44	14 (31.82)	18 (40.91)	12 (27.27)	72.73

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

2.2 两组治疗前后心功能指标变化情况对比

两组治疗后的左心室舒张期末内径、左心室收缩期末内径均较治疗前显著降低，而左心室射血分数及 6 min 步行试验均较治疗前明显增加(*P<0.05*)，且观察组左心室舒张期末内径、左心室收缩期末内径明显低于对照组，左心室射血分数及 6 min 步行试验显著高于对照组(*P<0.05*)。

2.3 两组治疗前后血清 hs-CRP、TNF-α 和 IL-6 水平比较

治疗后，两组血清 hs-CRP、TNF-α 和 IL-6 水平均较治疗前不同程度降低，且观察组血清 hs-CRP、TNF-α 和 IL-6 水平明显低于对照组(*P<0.05*)。

2.4 两组治疗前后血清 N 端脑钠肽前体水平对比

两组治疗后的血清 NT-proBNP 水平均较治疗前明显降低

(*P<0.05*),且观察组明显低于对照组(*P<0.05*),见表 4。

表 2 两组治疗前后心功能指标变化情况对比($\bar{x}\pm s$)

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

Groups	n		LVEDD (mm)	6MWT (m)	LVEF (%)	LVEDD (mm)
Observation group	44	Before treatment	50.27 ± 11.38	403.79 ± 126.38	36.57 ± 6.23	46.18 ± 11.27
		After treatment	40.13 ± 11.32*#	521.37 ± 132.94*#	49.38 ± 7.14*#	35.64 ± 10.09*#
Control group	44	Before treatment	51.49 ± 10.23	404.21 ± 123.79	36.14 ± 6.35	47.23 ± 10.65
		After treatment	45.32 ± 10.28#	465.38 ± 130.71#	42.33 ± 8.14#	40.28 ± 9.74#

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

表 3 两组治疗前后血清 hs-CRP、TNF-α 和 IL-6 水平对比($\bar{x}\pm s$)

Table 3 Comparison of the serum levels of hs-CRP, TNF-α and IL-6 between two groups before and after treatment ($\bar{x}\pm s$)

Group	n		hs-CRP (mg/L)	TNF-α (pg / mL)	IL-6(pg / mL)
Observation group	44	Before treatment	47.93 ± 3.12	25.47 ± 1.98	184.39 ± 12.65
		After treatment	12.45 ± 2.78*#	11.36 ± 1.25*#	57.62 ± 10.32*#
Control group	44	Before treatment	47.52 ± 3.85	25.13 ± 2.07	183.26 ± 13.41
		After treatment	23.69 ± 1.48#	17.82 ± 1.68#	98.31 ± 11.49#

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

表 4 两组治疗前后血清 N 端脑钠肽前体水平对比($\bar{x}\pm s$,pg/mL)

Table 4 Comparison of the serum levels of NT-proBNP between two groups before and after treatment ($\bar{x}\pm s$, pg/mL)

Groups	n	Before treatment	After treatment
Observation group	44	2283.41 ± 197.42	1327.49 ± 167.25#*
Control group	44	2285.93 ± 204.38	1873.42 ± 131.92#

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

3 讨论

慢性心力衰竭是指因受到瓣膜病、冠心病、高血压、肺心病、基因突变、血流动力负荷过重、心肌病以及心肌梗死等各种因素影响而造成心功能降低、静脉回流和心脏射血障碍,进而导致周围组织灌注不足、体循环和肺循环瘀血,患者主要表现为乏力、呼吸困难和液体潴留等[9-11]。

传统的正性肌力药如多巴胺、米力农和西地兰等药物,虽具有较好的强心效果,但是会增加心肌耗氧量,影响心肌舒张,导致恶性心律失常等不良反应。作为一种新型的正性肌力药,左西孟旦具有抗炎、神经内分泌以及抗凋亡等多种功能,可以有效抑制磷酸二酯酶、钙增敏以及开放钾离子通道,能通过细胞因子和神经内分泌等途径对心肌重构进行强有效的阻断,从而改善慢性心力衰竭患者的预后[15-18]。左西孟旦还可以通过活化 ATP 敏感型钾离子通道,降低慢性心力衰竭患者的肺毛细血管楔嵌压、肺动脉压以及总外周血管阻力,使心脏前负荷和后负荷下降,进而明显增加心排血量以及每搏输出量,但不会增加心肌耗氧量及心率,并且可以改善患者的血流动力学状态[19-22]。螺内酯能有效降低心脏负荷,改善患者的心脏舒张功能,抑制醛固酮对肾及心等靶器官所造成的不利于心功能的效应,还可以改善血管内皮功能,促进内皮一氧化氮的合成,从而发挥抗肾、心纤维化的功能[12-14]。本研究结果显示与单纯口服螺内酯的患者相比,左西孟旦联合螺内酯治疗的慢性心力衰竭患者临床总有效率显著升高,与 Babaev M A 等[23]的研究结果相一致。

炎症反应在慢性心力衰竭发生和发展过程中的心肌细胞凋亡、坏死、重塑、血管内皮受损以及氧化应激等多种细胞活动的调控中具有重要作用,会最终引发心衰程度加重[24-26]。炎性细胞因子是引起心肌肥厚、心室重构、心血管恶性事件以及心肌组织细胞凋亡的重要诱因。本研究结果显示左西孟旦联合螺内酯治疗的慢性心力衰竭患者治疗后血清 hs-CRP、TNF-α 和 IL-6 水平较单纯口服螺内酯的患者降低更为明显,表明螺内酯联合左西孟旦可更为有效地减轻慢性心力衰竭患者的炎症反应,进而减轻组织损伤,改善患者预后。心力衰竭患者的心肌结构和心肌功能由于受到各种因素的影响而发生改变,进而使泵血功能降低或心室充盈,心室重构是慢性心衰患者发生以及发展的重要病理生理基础。NT-proBNP 具有半衰期长、结构稳定以及受干扰小等多种优点,慢性心力衰竭患者的血浆 NT-proBNP 水平可以有效反映心功能的失代偿程度[27-30]。本研究中,左西孟旦联合螺内酯治疗的慢性心力衰竭患者治疗后血清 N 端脑钠肽前体水平较单纯口服螺内酯的患者明显降低,提示左西孟旦联合螺内酯治疗可以较单用螺内酯治疗更有效改善慢性心力衰竭患者的心室重构。抑制机体心室重构以及炎症反应可能是左西孟旦联合螺内酯提高慢性心力衰竭患者临

床疗效的主要作用机制。

综上所述,左西孟旦联合螺内酯治疗慢性心力衰竭患者可能显著提高其临床疗效,可能与其有效改善患者的心功能以及心室重构、减轻机体炎症反应有关。

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