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左西孟旦联合沙库巴曲缬沙坦钠对慢性心衰患者血流动力学和运动能力的影响*

魏莉娜 王月平 朱秋霞 任星星 贾利清

（内蒙古医科大学第三附属医院心血管内科 内蒙古 包头 014010）

摘要 目的:探讨左西孟旦联合沙库巴曲缬沙坦钠(诺欣妥)对慢性心衰患者血流动力学和运动能力的影响。**方法:**2018 年 1 月至 2019 年 5 月选择在本院心内科诊治的慢性心衰患者 80 例,根据随机数字表法分为联合组 50 例,对照组 30 例。两组入院后均进行常规治疗,在此基础上,对照组给予沙库巴曲缬沙坦钠治疗,联合组给予沙库巴曲缬沙坦钠联合左西孟旦治疗,两组都治疗观察 1 个月,记录血流动力学和运动能力的变化情况。**结果:**治疗后联合组的总有效率显著高于对照组(98.0 % vs 80.0 %,P<0.05)。治疗后联合组的总有效率显著高于对照组(98.0 % vs 80.0 %,P<0.05)。两组治疗前(left ventricular ejection fraction,LVEF)值和(Left ventricular end-systolic diameter,LVSD)值比较无统计学意义(P>0.05),治疗 1 个月后,两组的的 LVEF 值显著高于治疗前,LVSD 值显著低于治疗前(P<0.05),且上述指标的变化联合组更为显著(P<0.05)。两组治疗后的 6 min 步行距离都显著高于治疗前(P<0.05),且联合组也显著高于对照组(P<0.05)。**结论:**左西孟旦联合沙库巴曲缬沙坦钠治疗慢性心衰能改善患者的血流动力学状况和运动能力,从而提高治疗疗效。

关键词:左西孟旦;沙库巴曲缬沙坦钠;慢性心衰;血流动力学;运动能力

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Effects of Levosimendan Combined with Sacubitril Valsartan on Hemodynamics and Exercise Capacity in Patients with Chronic Heart Failure*

WEI Li-na, WANG Yue-ping, ZHU Qiu-xia, REN Xing-xing, JIA Li-qing

(Department of Cardiovascular Medicine, the Third Affiliated Hospital of Inner Mongolia Medical University, Baotou, Inner Mongolia, 014010, China)

ABSTRACT Objective: To investigate the effects of Levosimendan combined with Sacubitril Valsartan on hemodynamics and exercise capacity in chronic heart failure patients. **Methods:** From January 2018 to May 2019, 80 patients with chronic heart failure who were diagnosed and treated in in the Department of Cardiology of our hospital were enrolled and were divided into the combination group (50 cases) and the control group (30 cases) accorded to the random number table method. After the two groups were admitted routine treatment, on the basis of this, the control group was treated with Sacubitril Valsartan, the combination group was treated with Levosimendan combined with Sacubitril Valsartan. The two groups were treated for 1 month, and the changes of hemodynamics and exercise capacity were recorded. **Results:** The total effective rate of the combination group after treatment was significantly higher than that of the control group (98.0% vs 80.0%, P<0.05). There were no significant differences in the values of left ventricular ejection fraction (LVEF) and (Left ventricular end-systolic diameter, LVSD) between the two groups (P>0.05). After 1 month of treatment, the LVEF values of the two groups after treatment were significantly higher, and the LVSD values were significantly lower (P<0.05), and the change of the above indicators was more significant in the combination group (P<0.05). The 6-minute walking distance after treatment were significantly higher than that before treatment (P<0.05), and the combination group were also significantly higher than the control group (P<0.05). **Conclusion:** Levosimendan combined with Sacubitril Valsartan in the treatment of chronic heart failure can improve the hemodynamics and exercise capacity of patients, and thus improve the therapeutic effect.

Key words: Levosimendan; Sacubitril Valsartan; Chronic heart failure; Hemodynamics; Exercise capacity

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前言

心力衰竭(heart failure,HF)简称心衰,是各种心脏疾病导致射血功能受损,心排血量不能满足机体组织需要而表现为呼

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作者简介:魏莉娜(1973-),女,本科,副主任医师,研究方向:起搏与电生理,电话:13039566628,E-mail:Weilina19731115@163.com

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吸困难和乏力的一组综合征[1,2]。心衰是心血管疾病的终末阶段，在我国具有发病率高与死亡率高等特征，当前在我国仍以每年约 50 万的速度增长，5 年病死率与恶性肿瘤相当[3,4]。当前治疗该病的药物比较多，不过长期应用利尿剂容易出现药物抵抗；而正性肌力药物虽可增强心肌的收缩力，但是也可能增加心律失常的发生率[5,6]。沙库巴曲缬沙坦钠（诺欣妥）由沙库巴曲和缬沙坦按 1:1 组成的的血管紧张素受体脑啡肽酶抑制剂，能抑制多种内源性神经内分泌以及细胞因子的表达，从而减轻心肌细胞的损伤[7-9]。左西孟旦是一种钙离子增敏剂，可增强心肌收缩力，主要结合心肌细胞细肌丝上的肌钙蛋白来增加心肌对钙离子的敏感性，从而发挥扩张血管的作用[10-12]。该药在临床应用中不会增加心肌耗氧量，可改善患者的血流动力学状况，还可以改善患者的肾脏功能[13,14]。左西孟旦和沙库巴曲缬沙坦钠单独在心衰的应用十分常见，但是二者的联合应用国内外比较少见。本文通过分析了，推测二者联合应用可能是通过改变患者的血流动力学和运动能力，从而对慢性心衰患者发挥的作用，提高治疗疗效。现总结报告如下。

1 资料与方法

1.1 研究对象

2018 年 1 月至 2019 年 5 月选择在本院心内科诊治的慢性心衰患者 80 例作为研究对象，纳入标准：符合慢性心衰的诊断标准[15]；入院时 NYHA 心功能Ⅱ级或以上；本院伦理委员会批准了此次研究；患者签署了知情同意书；左室射血分数≤ 40 %，左室舒张末期内径≥ 55 mm。排除标准：对左西孟旦或其辅料过敏者；患者或家属拒绝本次研究者；严重肝、肾功能障碍患者；既往有室性心动过速、心室颤动等恶性心律失常病史患者。

根据随机数字表法分为联合组 50 例，对照组 30 例，两组的一般资料比较无差异（P>0.05）。见表 1。

表 1 一般资料对比

Table 1 Comparison of general data

Groups	n	Gender (Male/ Female)	Age (old)	BIM (kg/m^2)	Course of disease (year)	Heart function classification (Ⅱ/Ⅲ)
Combination group	50	32/18	56.02± 4.14	22.48± 1.29	2.04± 0.33	31/19
Control group	30	20/10	55.92± 3.19	22.10± 1.02	2.15± 0.22	20/10

1.2 治疗方法

两组患者入院后，均给予常规的抗心衰治疗，包括去除诱因、限制液体及钠的摄入量，规范的给予血管扩张剂、血管紧张素转化酶抑制剂、醛固酮、利尿剂和阿司匹林抗凝等药物。同时嘱咐患者充分休息，减少活动。

对照组：在常规治疗的基础上，给予沙库巴曲缬沙坦钠（国药准字 J20171054，北京诺华制药有限公司）治疗，每次口服 50 mg，1 次 /d。

联合组：在对照组治疗的基础上给予左西孟旦治疗，左西孟旦注射液（齐鲁药业有限公司生产，国药准字 H20100043），初始剂量为 6-12 μg/ kg，静脉推注 10 min；然后以 0.1 μg/(kg·min) 静脉滴注 24 h。

两组都治疗观察 1 个月。

1.3 观察指标

(1)疗效标准[16]：(有效 + 显效)/ 组内例数× 100.0%= 总有效率。显效：临床症状消失，心功能提高Ⅱ级以上。有效：症状缓解，心功能改善Ⅰ级。无效：症状无改变或恶化。(2)血流动力学：在治疗前后采用多功能彩色多普勒诊断仪检测左室收缩末径 (Left ventricular end-systolic diameter，LVSD)、左室射血分数值 (left ventricular ejection fraction，LVEF)等指标。(3)运动能力：在治疗前后进行 6 min 步行试验，由同一名经验丰富的医师进行判定。

1.4 统计方法

采用 SPSS19.00，计量数据以（$\bar{x}\pm s$），对比采用 t 检验；计数数据以%表示，对比用卡方分析，检验水准为 α=0.05，以 P<0.05 为有统计学意义。

2 结果

2.1 治疗后两组的基本症状的改善情况

治疗后，两组大部分患者症状消失，心功能提高。

2.2 总有效率对比

联合组的总有效率为 98.0 %，显著高于对照组的 80.0 % (P<0.05)。见表 2。

2.3 血流动力学变化对比

两组治疗前 LVEF 值和 LVSD 值比较无统计学意义（P>0.05），治疗 1 个月后，两组的的 LVEF 值显著高于治疗前，LVSD 值显著低于治疗前（P<0.05），且上述指标的变化联合组更为显著 (P<0.05)。见表 3。

表 2 总有效率对比(例，%)

Table 2 Comparison of total efficiency (n, %)

Groups	n	Excellence	Effective	Inavail	Total effective rate
Combination group	50	45	4	1	49(98.0)*
Control group	30	10	14	6	24(80.0)

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

表 3 治疗前后血流动力学变化对比($\bar{x}\pm s$)

Table 3 Comparison of hemodynamic changes before and after treatment ($\bar{x}\pm s$)

Groups	n	LVEF(%)		LVSD(mm)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Combination group	50	26.45± 1.88	44.56± 2.11*#	34.87± 2.19	25.98± 2.11*#
Control group	30	26.98± 2.00	38.90± 2.87*	34.78± 2.67	30.11± 2.81*

Note: Compared with the same group pretherapy, *P<0.05; compared with the control group post-treatment , #P<0.05.

2.4 6 min 步行距离对比

两组治疗后的 6 min 步行距离都显著高于治疗前(P<0.05)，且联合组更显著(P<0.05)。见表 4。

表 4 治疗前后 6 min 步行距离对比(m,$\bar{x}\pm s$)

Table 4 Comparison of 6 min walking distance before and after treatment (m, $\bar{x}\pm s$)

Groups	n	Pretherapy	Post-treatment
Combination group	50	332.94± 34.10	410.87± 42.91*#
Control group	30	330.87± 45.01	387.09± 25.77*

3 讨论

慢性心衰是一组复杂的临床综合征，是由于任何心脏结构或功能的异常导致心室射血受损。该病患者的预后不良，5 年病死率与恶性肿瘤相当，可会对患者的生活质量造成严重影响[17,18]。慢性心衰发作时，神经内分泌系统长期的过度兴奋可激活释放内源性神经内分泌以及细胞因子，从而加重机体血流动力学的紊乱、心肌细胞的损伤和心功能的下降，最终形成恶性循环[19,20]。沙库巴曲缬沙坦钠通过抑制血管紧张素Ⅱ受体的表达，发挥降低心脏前后负荷、抗心衰、改善心室重构等多重作用[21]。左西孟旦是钙离子增敏剂，可通过抗炎、扩血管、正性肌力等多种作用等途径缓解病理条件下心肌收缩功能失调。该药的半衰期约 1-1.5 h，故停止给药若干天后仍能保持良好血流动力学效应[22,23]。本研究显示治疗后联合组的总有效率为 98.0 %，显著高于对照组的 80.0 %；两组治疗后的 LVEF 值高于治疗前，LVSD 值低于治疗前，治疗后联合组与对照组对比差异也有统计学意义，表明联合用药能改善患者的血流动力学状况，提高治疗效果。特别是左西孟旦能延长肌动蛋白和肌凝蛋白纤维的相互作用时间，降低外周血管阻力，减轻心肌损害，使细胞膜超极化，改善心衰时期的血流动力学与心功能异常情况[24,25]。

心室重构是心衰发生发展的基本病理机制，不过心衰症状的出现发生在心室重构一段时期之后，且疾病的进展是不可逆的过程[26,27]。并且多数患者的的运动能力明显受限，症状严重，对治疗缺乏耐受性，多需要反复入院治疗[28]。本研究显示两组治疗后的 6 min 步行距离都显著高于治疗前，联合组也显著高于对照组，表明左西孟旦的应用能改善患者的运动能力。主要在于该药可增强心肌收缩力，减少神经内分泌激活及内皮素 -1 的释放，提高心脏输出量，减轻心脏的前后负荷，从而有利于患者运动能力的改善[29,30]。

不过本研究也存在一定的缺陷，研究入选的样本量较少，治疗可能存在一定程度的选择偏倚，将在下一步进行深入分析。同时对于两药联合应用的作用机制没有具体的研究，后续需要采用基础研究的方法，建立心衰的动物模型，探究左西孟旦联合沙库巴曲缬沙坦钠的治疗机制，为以后的用药和治疗提供跟更加准确的治疗路线。

总之，左西孟旦联合沙库巴曲缬沙坦钠治疗慢性心衰能改善患者的血流动力学状况和运动能力，从而提高治疗疗效。

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