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左西孟旦联合曲美他嗪对心衰介入治疗术后患者血清 galectin-3 和 syndecan-4 表达水平及心功能的影响 *

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摘要 目的：探讨左西孟旦联合曲美他嗪对心衰（heart failure，HF）介入治疗术后患者血清半乳糖凝集素 3（galectin-3）和人多配体蛋白聚糖 4（syndecan-4）表达水平及心功能的影响。**方法：**2018 年 9 月到 2021 年 1 月选择在本院完成介入治疗术的心衰患者 108 例，根据随机信封抽签原则把其分为联合组与对照组各 54 例。对照组给予左西孟旦治疗，联合组给予左西孟旦联合曲美他嗪治疗，两组都治疗观察 1 个月。**结果：**治疗后联合组的总有效率为 98.1%，高于对照组的 88.9%（*P*<0.05）。两组治疗后的左心室舒张末期内径（Left ventricular end diastolic diameter，LVEDD）、左心室收缩末期内径（Left ventricular end systolic diameter，LVESD）都低于治疗前（*P*<0.05），联合组低于对照组（*P*<0.05）。两组治疗后的血清 galectin-3 和 syndecan-4 含量低于治疗前（*P*<0.05），联合组低于对照组（*P*<0.05）。治疗后随访 6 个月，联合组的再住院率与死亡率为 9.3%和 3.7%，低于对照组的 27.8%和 14.8%（*P*<0.05）。**结论：** 左西孟旦联合曲美他嗪对心衰介入治疗术后患者的应用能抑制血清 galectin-3 和 syndecan-4 表达水平，改善患者的心功能，提高治疗效果，降低患者的随访再住院率与死亡率。

关键词：左西孟旦；曲美他嗪；心力衰竭；人多配体蛋白聚糖 4；半乳糖凝集素；心功能

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The Effects of Levosimendan Combined with Trimetazidine on Serum Galectin-3 and Syndecan-4 Expression and Cardiac Function in Patients with Heart Failure after Interventional Therapy*

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ABSTRACT Objective: To investigate the effects of levosimendan combined with trimetazidine on serum galectin-3 and syndecan-4 expression and cardiac function in patients with heart failure after interventional therapy. **Methods:** From September 2018 to January 2021, 108 cases of patients with heart failure who completed interventional therapy in Department of Cardiovascular Medicine, Shaanxi Provincial People's Hospital were selected and were divided into the combination group and levosimendan group with 54 cases each groups according to the principle of random envelope drawing. The levosimendan group were given levosimendan treatment, and the combination group were given levosimendan combined with trimetazidine treatment. Both groups were treated and observed for 1 month. **Results:** After treatment, the total effective rate of the combination group were 98.1%, which were higher than 88.9% of the levosimendan group (*P*<0.05). After treatment, the left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) of the combination group and the levosimendan group were lower than before treatment (*P*<0.05), and the combination group were lower than the levosimendan group (*P*<0.05). Serum galectin-3 and syndecan-4 levels after treatment in the the combination group and the levosimendan group were lower than before treatment (*P*<0.05), and the combination group were lower than the levosimendan group (*P*<0.05). Followed-up for 6 months after treatment, the rehospitalization rate and mortality rate of the combination group were 9.3% and 3.7%, which were lower than the 27.8% and 14.8% of the levosimendan group (*P*<0.05). **Conclusion:** The application of levosimendan combined with trimetazidine in patients with heart failure after interventional therapy can inhibit the expression of serum galectin-3 and syndecan-4, improve the patient's cardiac function, improve the treatment effect, and reduce the follow-up and rehospitalization of the patient Rate and mortality.

Key words: Levosimendan; Trimetazidine; Heart failure; Human polyligand proteoglycan 4; Galectin; Cardiac function

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前言

心力衰竭(heart failure,HF)简称心衰,是一种表现为神经内分泌激活、心功能受损、周身血流分布异常的临床综合征[1,2]。该病是缺血性心肌病发展到一定阶段而出现临床疾病,多伴随有胸痛发作。心衰的具体发病机制还不明确,病理特征涉及冠状动脉狭窄或闭塞、心肌细胞缺血或缺氧而变性、心肌收缩功能减退、心腔扩大等[3,4]。有研究显示有临床症状的心衰患者 5 年生存率与恶性肿瘤相仿,且多数患者伴随有运动耐力下降,可能是与患者病程进展过程中全身肌肉功能受损致体力活动受限有关,为此在对患者进行治疗的同时要积极提高患者的运动耐力[5]。冠状动脉介入手术(percutaneous Coronary intervention,PCI)为心衰的标准治疗方法,但是在术后需要配合合理的药物治疗[6]。曲美他嗪可阻断脂肪酸氧化,减少心肌耗氧量,从而能改善患者的能量代谢状况[7]。左西孟旦为一种新型的正性肌力药,可扩张冠状动脉血管及外周血管,也可以增强心肌收缩力,改善血流动力学状态,扩张冠状动脉血管及外周血管,同时也具有保护缺血心肌的作用[8,9]。半乳糖凝集素 -3(galectin-3)是由氨基酸末端区和羧基末端糖类识别区组成的多肽,可存在于细胞质、细胞核、细胞表面中,属凝集素蛋白家族成员,与心血管疾病的发生与发展有一定的相关性[10,11]。人多配体蛋白聚糖 4(syndecan-4)可以与血管内皮生长因子结合,可参与人体细胞生长分化凋亡、血管损伤修复等多种过程[12,13]。本文具体探讨了左西孟旦联合曲美他嗪对心衰介入治疗术后患者血清 galectin-3 和 syndecan-4 表达水平及心功能的影响,以明确两者联合使用的效果与机制。

1 资料与方法

1.1 研究对象

2018 年 9 月到 2021 年 1 月选择在陕西省人民医院心血管内一科完成介入治疗术的心衰患者 108 例,纳入标准:心功能分级Ⅱ-Ⅳ级,符合心衰的诊断标准;冠状动脉造影显示冠状动脉主要血管狭窄程度≥ 75%;患者签署了知情同意书;顺利完成冠状动脉介入手术;左心室射血分数(Left ventricular ejection fraction,LVEF)≤ 40%;年龄 20-75 岁;均能按医嘱正规服药;言语正常,有一定的理解能力。排除标准:活动性出血或有严重出血倾向等介入治疗术禁忌者;瓣膜病、心肌炎等其他原因所至心衰患者;严重肝肾功能不全患者;妊娠与哺乳期妇女;对所用的药物过敏及不良反应太大不能耐受者。

根据随机信封抽签原则把患者分为联合组与左西孟旦组各 54 例,两组患者的心功能分级、介入治疗时间、病变血管支数等对比差异无统计学意义(P>0.05)。

表 1 一般资料

Table 1 General Information

Groups	n	Gender (male/female)	Age (years)	Number of diseased vascular branches (branches)	Interventional treatment time (min)	Body Weight Index (kg/m^2)	Heart function Classification (Level/level)
Combination group	54	28/26	58.14± 4.18	1.89± 0.24	51.38± 2.57	22.74± 1.47	20/19/15
Levosimendan group	54	29/25	58.25± 3.17	1.90± 0.18	51.22± 3.17	22.87± 1.11	21/18/15

1.2 治疗方法

左西孟旦组:给予左西孟旦治疗,左西孟旦注射液(国药准字 H20100043,齐鲁制药有限公司),起始剂量 12 μg/ kg 静脉推注,然后以 0.1 μg·kg^{-1}·min^{-1} 的速度静脉滴注,1 h 后可调整为 0.15-0.2 μg·kg^{-1}·min^{-1},持续滴注 24 h。

联合组:给予曲美他嗪治疗,口服曲美他嗪片(国药准字 H20073709,江苏吴中医药集团有限公司)20 mg,3 次 /d。

两组都治疗观察 1 个月,在治疗过程中都对症给予心肌缺血(硝酸酯)、血管紧张素转化酶抑制剂(卡托普利)、抗血小板(阿司匹林)、β 受体阻滞剂(美托洛尔)、调脂(他汀类药物)、醛固酮受体拮抗剂(螺内酯)等基础治疗。

1.3 观察指标

(1)疗效标准:总有效率 =(显效 + 有效)/ 总数× 100%。显效:症状及体征基本控制,LVEF≥ 50%;有效:症状及体征有所好转,LVEF 在 45%-49%或 LVEF 提高 3%-5%;无效:无达到上述标准甚或恶化。(2)所有患者在治疗前后采集患者的空腹肘静脉血 3-5 mL,室温放置 30 min 后,离心分离上层血清(1500-2000 r/min 离心 5 min),采用酶联免疫吸附剂法检测血清 galectin-3 和 syndecan-4 含量。(3)在治疗前后采用飞利浦超声诊断仪测定患者的 LVESD 和 LVEDD,可判断患者的心功能改善情况。(4)治疗后随访 6 个月,记录患者的再住院率及死亡率。

1.4 统计方法

数据录入采用 Excel 2010,统计软件为 SPSS24.00,计数数据以率(%)表示(对比为卡方 x^2 检验),计量资料以均数± 标准差表示(对比为 t 检验),检验水准为α=0.05。

2 结果

2.1 总有效率

治疗后,联合组的总有效率显著高于左西孟旦组(P<0.05)。见表 2。

2.2 心功能变化

两组治疗后的 LVESD 与 LVEDD 值都低于治疗前(P<0.05),联合组低于左西孟旦组(P<0.05)。见表 3。

2.3 血清 galectin-3 和 syndecan-4 含量变化

两组治疗后的血清 galectin-3 和 syndecan-4 含量低于治疗前(P<0.05),联合组低于左西孟旦组(P<0.05)。见表 4。

2.4 随访情况

治疗后随访 6 个月,联合组的再住院率与死亡率均显著低于左西孟旦组(P<0.05)。见表 5。

表 2 两组治疗总有效率对比[例(%)]

Table 2 Comparison of total treatment efficacy between the two groups[n(%)]

Groups	n	Excellence	Effective	Invalid	Total effective rate
Combination group	54	49	4	1	53(98.1%)*
Levosimendan group	54	34	14	6	48(88.9%)

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

表 3 两组治疗前后心功能变化对比(mm)

Table 3 Comparison of cardiac function changes before and after treatment in the two groups (mm)

Groups	n	LVESD		LVEDD	
		Before treatment	After treatment	Before treatment	After treatment
Combination group	54	55.25± 7.48	46.38± 5.15*#	66.72± 5.78	54.76± 5.58*#
Levosimendan group	54	55.10± 5.68	51.02± 7.18#	66.92± 6.10	59.78± 6.15#

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

表 4 两组治疗前后血清 galectin-3 和 syndecan-4 含量变化对比

Table 4 Comparison of serum galectin-3 and syndecan-4 before and after treatment in the two groups

Groups	n	galectin-3(μg/L)		syndecan-4(ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Combination group	54	15.62± 1.52	10.24± 1.47*#	5.49± 0.32	3.89± 0.76*#
Levosimendan group	54	15.48± 2.03	13.48± 2.00#	5.51± 0.28	4.34± 0.76#

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

表 5 两组随访情况对比[例(%)]

Table 5 Comparison of the follow-up conditions between the two groups[n(%)]

Groups	n	Rehospitalization rate	Death rate
Combination group	54	5(9.3%)*	2(3.7%)*
Levosimendan group	54	15(27.8%)	8(14.8%)

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

3 讨论

心血管疾病死亡率一直位居各病因之首,且具有很高的致残率,占居民疾病死亡构成的 35.0%以上[14]。其中心衰为各种心脏疾病的终末阶段,伴随有血流动力学负荷过重、大量炎性因子释放、心脏细胞受损、心室泵血和充盈功能受损等[15]。该病在临床上多表现为乏力、水肿等症状,可反复发作,且病情顽固。心衰的治疗目的是延缓和防止心肌重构的发展, 改善临床症状,降低病死率[16]。左西孟旦为一种新型的正性肌力药,可直接作用于肌钙蛋白 C 导致其发生构象改变,在不增加舒张期心肌细胞内的钙离子浓度的基础上增加心肌的收缩力[17];并且其也可产生扩血管作用,通过稳定线粒体膜,减轻心脏的后负荷,增加心脏微循环灌注;改善血流动力学,发挥抗缺血缺氧的心肌细胞保护作用[18]。

本研究显示治疗后联合组的总有效率为 98.1%,高于左西孟旦组的 88.9%(P<0.05); 两组治疗后的 LVESD 与 LVEDD 值都低于治疗前,联合组低于左西孟旦组(P<0.05),表明:左西孟旦联合曲美他嗪在介入治疗术后心衰患者的应用能持续促进改善心功能,从而提高总体治疗效果。结合 Ussher JR[19]等研究分析,曲美他嗪为代谢类细胞保护剂,能强化葡萄糖有氧代谢,也能使心肌细胞代谢得到良好调节,可抑制 3- 酮脂酰辅酶 A 硫解酶的活性,加速三磷酸腺苷分泌,从而有效改善心肌舒缩功能。另外,陈秋玲等[20]研究显示:与左西孟旦的联合使用可发挥协同作用,从而可减轻心脏前后负荷,对促进心功能的改善具有重要价值,与本研究结果一致。

血清 galectin-3 是人体内的一种促炎因子, 其可刺激和活化单核巨噬细胞、纤维细胞发挥促炎作用[21,22]。心血管疾病患者的血清 galectin-3 水平明显高于正常人群,且 galectin-3 水平与心血管疾病的心功能分级、预后具有一定的相关性[23]。syndecan-4 细胞外基质的主要组成成分, 也是心脏成纤维细胞的细胞膜所表达的跨膜蛋白聚糖[24]。syndecan-4 可调节心脏成纤维细胞表型和功能及心肌纤维化,也可结合细胞因子、生长因子、免疫细胞黏附蛋白,从而参与心脏纤维化信号转导[25]。当机体出现心肌损伤或心室压力增高时,心脏成纤维细胞可大量释放 syndecan-4,从而导致心肌纤维化,导致疾病恶化。同时 syndecan-4 介导的炎症调节作用与心肌重构作用, 也可能是导致心血管疾病患者致残与致死的重要原因之一[26,27]。本研究显示两组治疗后的血清 galectin-3 和 syndecan-4 含量低于治疗前

（P<0.05），联合组低于左西孟旦组（P<0.05），结合 Williams D M 等[28]研究分析：左西孟旦可抑制磷酸二酯酶的活性，可以快速有效提高患者的心肌收缩力、扩张外周血管，从而促进患者的心功能恢复。吴刚[29]和 Tian Y[30]等研究结果显示：曲美他嗪能有效改善患者的心肌能量代谢途径，可增加葡萄糖氧化反应，促使机体产生更多腺嘌呤核苷三磷酸，提高心肌细胞对氧的利用率，减少心肌脂肪氧化，从而增加心肌能量供给，有利于降低血清 galectin-3 和 syndecan-4 水平，减轻心室重构，促进改善患者的预后，与本研究结果一致。

多数心衰患者伴随多种合并症，存在心衰失代偿难以控制、病情进展快、致残率高、死亡率高、再住院率高等特点，使得预后一直不佳[31]。本研究显示治疗后随访 6 个月，联合组的再住院率与死亡率为 9.3%和 3.7%，低于左西孟旦组的 27.8%和 14.8%（P<0.05），结合相关研究[32-34]分析，曲美他嗪可有效降低机体的交感神经活性，提高心率变异性，从而有利于持续改善患者的预后。本研究也存在一定的不足，随访时间比较短，且没有设置单独应用曲美他嗪组，纳入患者的数量也比较少，将在后续研究中进行探讨。

综上所述，左西孟旦联合曲美他嗪对心衰介入治疗术后患者的应用能抑制血清 galectin-3 和 syndecan-4 表达水平，从而进一步改善患者的心功能，并降低患者的随访再住院率与死亡率，且其治疗效果较好，应广泛应用于临床。

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