·临床研究·

左西孟旦对老年射血分数保留型心力衰竭急性加重期患者的疗效

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【摘 要】 目的 探讨左西孟旦对老年射血分数保留型心力衰竭(HFpEF)急性加重期患者的治疗效果。**方法** 回顾性分析2016年1月至2019年12月于空军军医大学第一附属医院收治住院的52例HFpEF急性加重期病例的临床资料。根据是否接受了左西孟旦治疗将患者分为左西孟旦治疗组(26例)和对照组(26例),比较2组患者治疗1周后纽约心脏病协会(NYHA)心功能分级改善率(有效率),3、12个月内再住院率及治疗前后N末端脑钠肽前体(NT-proBNP)水平变化。采用SPSS 19.0统计软件进行数据分析。根据数据类型,分别采用 t 检验、*Wilcoxon* 秩和检验、χ^2 检验或 *Fisher* 确切概率法检验进行组间比较。**结果** 治疗1周后左西孟旦治疗组有效率显著高于对照组,3个月内再住院率显著低于对照组,差异均有统计学意义($P<0.05$);12个月内2组再住院率比较,差异无统计学意义($P>0.05$);治疗后2组NT-proBNP水平均显著降低($P<0.05$),但组间降幅差异无统计学意义($P>0.05$);NT-proBNP水平降低30%以上的比例比较,差异无统计学意义($P>0.05$)。**结论** 应用左西孟旦治疗老年HFpEF急性加重期患者,可明显减轻患者心力衰竭症状,改善心功能分级,降低短期内再住院风险,效果较好,安全性较高,而对远期再住院风险无显著影响。

【关键词】 老年人;射血分数保留型心力衰竭;左西孟旦;再住院率;N末端脑钠肽前体
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Efficacy of levosimendan in treatment of acute exacerbation of heart failure with preserved ejection fraction in the elderly

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【Abstract】 Objective To investigate the therapeutic effectiveness of levosimendan on acute exacerbation of heart failure with preserved ejection fraction (HFpEF) in the elderly. **Methods** A retrospective analysis was carried out in 52 elderly patients with acute exacerbation of HFpEF admitted to the First Affiliated Hospital of Air Force Medical University from January 2016 to December 2019. The patients were divided into the levosimendan treatment group (26 cases) and the control group (26 cases) according to whether they received levosimendan therapy. The improvement of New York Heart Association (NYHA) cardiac function classification (effective rate) 1 week after treatment, the rehospitalization rates within 3 and 12 months, and the changes of N-terminal pro-brain natriuretic peptide (NT-proBNP) before and after treatment were compared between the 2 groups. SPSS statistics 19.0 was used for data analysis. According to the distribution type, student's t test, *Wilcoxon* rank sum test, *Chi*-square test or *Fisher* exact probability test was performed for intergroup comparison. **Results** Compared with the control group, the levosimendan group had significantly higher effective rate after 1 week treatment ($P<0.05$) and lower readmission rate within 3 months ($P<0.05$). There was no statistical difference in the readmission rate within 12 months between the 2 groups ($P>0.05$). After treatment, the NT-proBNP levels were significantly decreased in both groups ($P<0.05$), but the difference was not statistically significant ($P>0.05$). After treatment, the proportion of patients whose NT-proBNP level was decreased by more than 30% in the two groups were compared, but no statistical difference was observed between the 2 groups ($P>0.05$). **Conclusion** Application of levosimendan in the treatment of acute exacerbation of HFpEF in the elderly can significantly alleviate the symptoms of heart failure, improve the heart function and reduce short-term readmission risk, with high safety, but has no obvious effect on long-term readmission risk.

【Key words】 aged; heart failure with preserved ejection fraction; levosimendan; readmission rate; N-terminal pro-brain natriuretic peptide

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射血分数保留型心力衰竭(heart failure with preserved ejection fraction, HFpEF)多见于高龄老人,是一种涉及全身多系统的复杂临床综合征,具有高异质性的多种表型,发病机制尚不明确[1],一线抗心力衰竭药物均无法有效改善其预后[2]。慢性HFpEF患者常因各种诱因急性加重。本研究旨在观察左西孟旦对老年HFpEF急性加重期患者的治疗效果,以期为老年HFpEF急性加重的临床治疗提供新的思路。

1 对象与方法

1.1 研究对象

回顾性分析2016年1月至2019年12月于空军军医大学第一附属医院住院治疗的52例老年射血分数保留型心力衰竭急性加重期患者的病历资料。依据《中国心力衰竭诊断和治疗指南2018》中HFpEF诊断标准[3]。纳入标准:(1)诊断为HFpEF,因急性加重住院;(2)年龄≥60岁;(3)纽约心脏病协会(New York Heart Association, NYHA)心功能分级Ⅲ~Ⅳ级;(4)心力衰竭稳定期规律服用基础抗心力衰竭药物;(5)住院期间接受了利尿、强心、扩血管治疗。排除标准:(1)严重心脏瓣膜病;(2)恶性肿瘤;(3)严重局部感染或系统性感染。

1.2 方法

52例患者中,将接受了左西孟旦治疗的患者分为左西孟旦治疗组(26例),未接受左西孟旦治疗的分为对照组(26例)。左西孟旦治疗方法为:左西孟旦注射液(齐鲁制药有限公司,国药准字H20100043,规格:每支5 ml:12.5 mg)5 ml配制成5%葡萄糖溶液50 ml,静脉泵入,初始负荷剂量为6~12 μg/kg,时间不少于10 min,之后以0.05~0.2 μg/(kg·min)泵速持续给药24 h。如果治疗前患者血压偏低,可以不给予负荷剂量。在负荷剂量及持续给药的起初30~60 min内,密切观察患者反应,监测血压和心率,调整泵速。

1.3 观察指标

3个月内及12个月内再住院情况,治疗前后NYHA心功能分级、N末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)水平、超声心动图左室射血分数(left ventricular ejection fraction, LVEF)、收缩期左心房左右径。治疗前后丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天冬氨酸氨基转移酶(aspartate aminotransferase, AST)、尿素、肌酐水平。

1.4 疗效评定标准

有效:治疗后心力衰竭症状减轻,经评估NYHA心功能分级改善Ⅰ级或Ⅰ级以上;无效:治疗后心力衰竭症状改善不明显或加重,经评估NYHA心功能分级无变化或恶化[4]。

1.5 统计学处理

采用SPSS 19.0统计软件进行数据分析。符合正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验;不符合正态分布的计量资料使用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用*Wilcoxon*秩和检验。计数资料以例数(百分率)表示,组间比较采用χ^2检验或*Fisher*确切概率法检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者一般资料比较

2组患者基线特征均衡性良好,差异无统计学意义(表1),具有可比性。

2.2 有效性指标

左西孟旦治疗组有效率高于对照组,3个月内再住院率低于对照组,差异均有统计学意义($P<0.05$);左西孟旦治疗组12个月内再住院率及治疗后NT-proBNP水平降低30%以上的比例与对照组比较,差异均无统计学意义($P>0.05$;表2)。治疗后,2组NT-proBNP水平变化值、LVEF变化值及收缩期左心房左右径变化值比较,差异均无统计学意义($P>0.05$;表3)。

2.3 安全性指标

2组患者ALT、AST、尿素、肌酐水平治疗前后变化值比较,差异均无统计学意义($P>0.05$;表4)。

3 讨 论

既往的研究表明,老年心力衰竭患者中有大约50%为HFpEF。HFpEF患者大多合并冠心病、高血压、糖尿病、慢性阻塞性肺疾病、肾功能不全等多系统慢病,死亡风险也随着共病负担的增加而增加[5]。有研究指出HFpEF诊断后12个月病死率达20%以上,5年病死率超过50%[6]。目前,对于HFpEF尚缺乏改善预后的治疗建议,主要是对症、营养支持和加强运动。

表 1 2 组患者基线资料比较

Table 1 Comparison of baseline data between two groups (n=26)

Item	Levosimendan group	Control group	P value
Demographics			
Male[n(%)]	18(69.2)	12(46.2)	0.254
Age(years, $\bar{x}\pm s$)	85.0±8.7	82.9±9.9	0.433
NYHA heart function classification[n(%)]			0.575
Class Ⅲ	10(38.5)	12(46.2)	
Class Ⅳ	16(61.5)	14(53.8)	
Basic illness[n(%)]			
Coronary heart disease	22(84.6)	23(88.5)	1.000
Atrial fibrillation	11(42.3)	12(46.2)	0.780
Hypertension	18(69.2)	19(73.1)	0.760
Diabetes mellitus	10(38.5)	10(38.5)	1.000
Hyperlipidemia	0(0.0)	3(11.5)	0.235
COPD	6(23.1)	3(11.5)	0.463
Anemia	12(46.2)	11(42.3)	0.780
OSAHS	0(0.0)	1(3.8)	1.000
Chronic renal insufficiency	9(34.6)	14(53.8)	0.163
Basic anti-heart failure medication[n(%)]			
ACEI	5(19.2)	3(11.5)	0.701
ARB	11(42.3)	6(23.1)	0.139
ARNI	8(30.8)	9(34.6)	0.768
β-blocker	15(57.7)	14(53.8)	0.780
MRA	19(73.1)	14(53.8)	0.150
SGLT-2I	1(3.8)	3(11.5)	0.603
Basic vital signs			
SBP(mmHg, $\bar{x}\pm s$)	129.7±20.6	130.5±23.7	0.896
DBP(mmHg, $\bar{x}\pm s$)	66.3±11.1	66.6±10.0	0.917
Heart rate(beats/min, $\bar{x}\pm s$)	74.6±11.2	76.9±14.0	0.508
Laboratory test			
White blood cell($\times10^9$/L, $\bar{x}\pm s$)	6.8±3.4	7.0±2.9	0.802
Red blood cell($\times10^{12}$/L, $\bar{x}\pm s$)	3.8±0.7	3.7±0.7	0.485
Platelets($\times10^9$/L, $\bar{x}\pm s$)	178.9±72.1	155.3±83.4	0.280
Hb(g/L, $\bar{x}\pm s$)	116.1±23.0	110.9±18.9	0.368
Albumin(g/L, $\bar{x}\pm s$)	35.4±5.3	34.5±4.4	0.547
ALT[IU/L, M (Q_1, Q_3)]	22.0(12.8,37.3)	19.0(12.0,27.8)	0.314
AST[IU/L, M (Q_1, Q_3)]	26.5(21.8,37.0)	25.0(18.0,29.3)	0.164
Urea[mmol/L, M (Q_1, Q_3)]	7.8(5.6,13.3)	8.0(7.0,15.6)	0.360
Creatinine[μmol/L, M (Q_1, Q_3)]	98.0(65.8,131.3)	118.5(96.0,137.8)	0.148
NT-proBNP[pg/ml, M (Q_1, Q_3)]	2929.5(1383.3,4917.3)	2766.5(1493.5,5003.3)	0.985
Echocardiography($\bar{x}\pm s$)			
LVEF(%)	54.1±4.0	54.8±6.2	0.612
Left atrial diameter S(mm)	40.5±5.9	41.0±7.0	0.764
Left ventricular long diameter S(mm)	64.3±6.5	63.0±8.2	0.526
Left ventricular long diameter D(mm)	74.4±6.2	72.7±7.7	0.377
Right atrial diameter S(mm)	39.5±7.8	37.9±5.1	0.394
Right ventricular diameter D(mm)	26.7±5.1	25.2±4.4	0.263
Interventricular septum thickness(mm)	10.5±1.5	10.3±1.3	0.622

NYHA: New York Heart Association; COPD: chronic obstructive pulmonary diseases; OSAHS: obstructive sleep apnea-hypopnea syndrome; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibition; MRA: mineralocor ticoid receptor antagonist; SGLT-2I: sodium-dependent glucose transporters 2 inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction. 1 mmHg=0.133 kPa.

表2 2组患者有效率、再住院率、NT-proBNP水平降低30%以上的比例情况比较

Table 2 Comparison of effective rate, readmission rate and proportion of NT-proBNP level reduction by >30% between two groups

[n=26, n(%)]

Item	Levosimendan group	Control group	χ^2	P value
Effective	14(53.8)	6(23.1)	5.200	0.023
Readmission within 3 months	9(34.6)	17(65.4)	4.923	0.027
Readmission within 12 months	19(73.1)	19(73.1)	0.000	1.000
NT-proBNP reduction by >30%	14(53.8)	10(38.5)	1.238	0.266

NT-proBNP: N-terminal pro-brain natriuretic peptide.

表3 2组患者治疗后NT-proBNP、LVEF、收缩期左心房左右径的变化情况比较

Table 3 Comparison of NT-proBNP, LVEF and systolic left-to-right diameter of left atrium changes after treatment between two groups

(n=26)

Item	Levosimendan group	Control group	P value
NT-proBNP[pg/ml, M (Q_1, Q_3)]	−829.6(−2246.0,37.4)	−509.5(−1878.7,70.8)	0.370
LVEF(%, $\bar{x}\pm s$)	1.2±4.4	−1.3±5.9	0.093
Systolic left-to-right diameter of left atrium (mm, $\bar{x}\pm s$)	1.3±5.4	−0.2±4.5	0.270

NT-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction.

表4 2组患者治疗后ALT、AST、尿素、肌酐水平的变化情况比较

Table 4 Comparison of ALT, AST, urea and creatinine level changes after treatment between two groups

[n=26, M (Q_1, Q_3)]

Item	Levosimendan group	Control group	P value
ALT(IU/L)	−1.5(−11.0,2.3)	0.0(−3.5,3.0)	0.204
AST(IU/L)	−2.5(−8.3,2.0)	0.0(−4.0,2.0)	0.423
Urea(mmol/L)	0.2(−2.0,3.1)	0.2(−0.6,2.3)	0.927
Creatinine(μmol/L)	1.5(−6.3,18.0)	0.0(−11,23.8)	0.673

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

老年慢性HFpEF患者常因血压升高、感染慢性阻塞性肺疾病急性加重、肾功能恶化等一个或多个诱因发生急性加重,需要住院治疗。根据容量负荷和外周组织灌注情况,给予利尿、扩血管等治疗[7]。HFpEF患者LVEF≥50%,原则上不需要强心治疗,但研究发现HFpEF患者不仅有心室舒张功能障碍,同时存在收缩功能障碍[8,9]。强心治疗可提高心肌收缩力,改善心力衰竭症状。如血压低于90 mmHg(1 mmHg=0.133 kPa),则首选正性肌力药[3]。

左西孟旦是一种钙离子增敏剂,通过与肌钙蛋白相结合,稳定钙离子诱导的心肌纤维蛋白空间构型,从而发挥正性肌力作用,而心率、心肌耗氧无明显变化,还可以激活三磷酸腺苷敏感的钾通道,使外周血管和冠状动脉扩张,改善肾血流,达到利尿效果,降低心脏负荷,改善心肌供血[10]。在急性失代偿心力衰竭治疗中,左西孟旦能快速、持久缓解心力衰竭症状[11]。在对晚期稳定慢性心力衰竭治疗中,左西孟旦可显著改善血流动力学,增加心输出量,降低总体外周阻力和平均动脉压[12]。左西孟旦独立于β肾上腺素能受体起作用,对服用β受体阻滞剂的患者疗效优于多巴胺、多巴酚丁胺[13]。持续性低血压存在时,去甲肾上腺素联合左西孟旦可增强心脏收缩力,同时保持足够的血压维持组织灌注[14]。在右心室衰竭和(或)肺动脉高压患者中,左西孟旦因其对肺血管系统的血管舒张作用而首选[13]。然而,左西孟旦治疗老年HFpEF急性加重期的研究报道比较少。

本研究从NYHA心功能改善、再住院率、NT-proBNP水平变化等方面回顾性评价了左西孟旦治疗HFpEF急性加重期患者的效果。在接受左西孟旦治疗后1周,左西孟旦治疗组心力衰竭症状明显缓解,心功能分级显著改善。2组NT-proBNP水平较治疗前均显著降低,但组间比较无显著差异,按NT-proBNP水平降低30%以上的比例比较,2组间差异无统计学意义。3个月内再住院率,左西孟旦治疗组明显低于对照组,表明左西孟旦在短期内能改善并稳定患者心功能,降低HFpEF患者再住院风险;但到12个月时,左西孟旦治疗组再住院率升高了1倍以上,与对照组相当,表明左西孟旦对HFpEF远期预后没有明显改善。2组患者治疗前后ALT、AST、尿素、肌酐水平变化值的组间比较均无显著差异,提示左西孟旦对患者肝功能、肾功能无明显影响,2组治疗期间未发生明显低血压和心率增快,提示在老年HFpEF患者中应用左西孟旦具有良好

的安全性。

综上,本研究结果显示,应用左西孟旦治疗老年 HFpEF 急性加重期患者,可快速减轻患者心力衰竭症状,改善心功能分级,降低短期内再住院风险,效果良好,安全性高,而对远期再住院风险无明显影响。

本研究属回顾性研究,易发生选择偏倚和信息偏倚,且因老年患者大多病情复杂,符合条件入选的样本量较少,结果有一定局限性,需要更大样本量的前瞻性研究进一步验证结论。

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