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注射用地尔硫卓联合前列地尔注射液对射血分数保留型心衰患者 心功能、血清炎症因子和氧化应激的影响*

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摘要 目的:注射用地尔硫卓联合前列地尔注射液对射血分数保留型心衰(HFpEF)患者心功能、血清炎症因子和氧化应激的影响。**方法:**选取2016年3月至2020年3月期间于齐都医院接受治疗的HFpEF患者108例,根据奇偶排序法分为对照组54例、研究组54例,对照组患者给予注射用地尔硫卓治疗,研究组患者给予注射用地尔硫卓联合前列地尔注射液治疗,疗程为2周。对比两组治疗2周后的疗效,记录两组治疗期间不良反应发生情况。对比两组治疗前、治疗2周后的二尖瓣舒张早期血流峰速度/心房收缩期二尖瓣口最大血流流速(E/A)以及二尖瓣舒张早期血流峰速度/二尖瓣环舒张早期运动峰速度(E/E'),B型尿钠肽(BNP)、C反应蛋白(CRP)、白细胞介素(IL)-6、巨噬细胞移动抑制因子(MIF)、鸟嘌呤(8-OHdG)、超氧化物歧化酶(SOD)、丙二醛(MDA)。**结果:**与对照组的总有效率75.93%(41/54)相比,研究组的总有效率92.59%(50/54)更高($P<0.05$)。研究组治疗2周后BNP、E/E'低于对照组,E/A高于对照组($P<0.05$)。研究组治疗2周后IL-6、CRP、MIF低于对照组($P<0.05$)。研究组治疗2周后8-OHdG、MDA低于对照组,SOD高于对照组($P<0.05$)。两组均未见明显不良反应发生。**结论:**注射用地尔硫卓联合前列地尔注射液能显著改善HFpEF患者心功能,改善机体血清炎症因子和氧化应激,安全有效。

关键词:注射用地尔硫卓;前列地尔注射液;射血分数保留型心衰;心功能;炎症因子;氧化应激

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Effects of Diltiazem for Injection Combined with Alprostadil Injection on Cardiac Function, Serum Inflammatory Factors and Oxidative Stress in Patients with Ejection Fraction Preserved Heart Failure*

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ABSTRACT Objective: To investigate the effects of diltiazem for injection combined with alprostadil injection on cardiac function, serum inflammatory factors and oxidative stress in patients with ejection fraction preserved heart failure (HFPEF). **Methods:** 108 HFPEF patients who were admitted and treated in Qidu hospital from March 2016 to March 2020 were selected, they were divided into control group of 54 cases, study group of 54 cases according to parity sorting method, patients in control group were treated with diltiazem for injection, patients in study group were treated with diltiazem for injection combined with alprostadil injection, the course of treatment was 2 weeks. The curative effects of two groups after 2 weeks of treatment were compared, the incidence of adverse reactions in the two groups was recorded. the peak velocity of mitral early diastolic flow/maximum flow velocity of atrial systolic mitral valve orifice (E/A) and peak velocity of mitral early diastolic flow/early diastolic blood flow velocity (E/E'), B-type natriuretic peptide (BNP), C-reactive protein (CRP), interleukin-6 (IL-6), macrophage migration inhibitory factor (MIF), guanine (8-OHdG), superoxide dismutase (SOD), malondialdehyde (MDA) were compared between the two groups before treatment, after 2 weeks of treatment. **Results:** Compared with 75.93% (41/54) of the total effective rate in control group, 92.59% (50/54) of the total effective rate in study group was higher ($P<0.05$). BNP and E/E' of study group were lower than those of control group, E/A was higher than control group after 2 weeks of treatment ($P<0.05$). IL-6, CRP, MIF in study group were lower than those of control group after 2 weeks of treatment ($P<0.05$). 8-OHdG, MDA in study group were lower than those in control group, SOD was higher than control group after 2 weeks of treatment ($P<0.05$). There was no obvious adverse reactions occurred in both groups. **Conclusion:** Diltiazem for injection combined with alprostadil injection can signifi-

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cantly improve cardiac function in patients with HFpEF, improve the body serum inflammatory factors and oxidative stress, which is safe and effective.

Key words: Diltiazem for injection; Alprostadil injection; Ejection fraction preserved heart failure; Cardiac function; Inflammatory factors; Oxidative stress

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前言

射血分数保留型心衰(HFpEF)是指由各种因素导致的心脏无法满足机体正常循环需求时,通过增加左心室充盈压为代价来满足这种需求,进而因为舒张功能异常造成左心室舒张末压升高,诱发肺静脉压升高,导致肺淤血,甚至引起心衰^[1-3]。HFpEF的主要临床症状表现为水肿、呼吸困难、乏力等,辅助检查显示左心室射血分数(LVEF)≥ 50%^[4]。据以往流行病学调查研究显示^[5],HFpEF多见于女性、高龄和高血压患者,是65岁以上人群中是最常见的心衰形式,约有85%的新发心衰患者属于HFpEF。现临床尚无有关HFpEF的统一治疗方案,多以肾素-血管紧张素系统拮抗剂、β受体阻滞剂、钙通道阻滞剂等药物进行基础对症治疗^[6]。地尔硫卓是钙离子通道阻滞剂的一种,可有效缓解HFpEF的临床症状,但疗效仍有提升空间^[7]。前列地尔为天然前列腺素类物质,具有改善微循环、扩张微小动静脉的功能^[8]。本研究观察了前列地尔注射液与注射用地尔硫卓联合治疗HFpEF的临床疗效,旨在为临床治疗提供数据支持。

1 资料与方法

1.1 一般资料

选取2016年3月至2020年3月期间于齐都医院接受治疗的HFpEF患者108例,纳入标准:(1)诊断标准参考《射血分数正常心力衰竭诊治的中国专家共识》^[9];(2)临床存在水肿、呼吸困难、乏力及进行性活动耐力减低者,LVEF≥ 50%,BNP>1000 pg/mL;(3)患者及其家属均知情本研究且签署同意书。排除标准:(1)心脏瓣膜病、缩窄性心包炎以及其他非心脏疾病;(2)对本次研究用药存在过敏症者;(3)左心室舒张功能异常即左室充盈压升高;(4)慢性阻塞性肺疾病合并右心功能衰竭者;(5)合并精神障碍,无法正常沟通交流者。根据奇偶排序法分为对照组54例、研究组54例,其中对照组男16例,女38例,年龄52~83岁,平均(71.59± 3.26)岁;体质量指数19~26 kg/m²,平均(23.41± 0.88)kg/m²;病程6个月~3年,平均(1.96± 0.27)年;原发病:冠心病21例,高血压心脏病33例;合并症:高血脂9例,糖尿病14例。研究组男18例,女36例,年龄54~82岁,平均(70.96± 4.13)岁;体质量指数20~26 kg/m²,平均(23.21± 0.94)kg/m²;病程8个月~4年,平均(1.91± 0.35)年;原发病:冠心病20例,高血压心脏病34例;合并症:高血脂11例,糖尿病12例。两组一般资料对比($P>0.05$),资料均衡可比。本研究已获齐都医院医学伦理委员会。

1.2 方法

两组患者入院后均给予吸氧,休息,限钠限水等一般治疗,并予抗血小板聚集、降低血压、减轻心脏负荷、控制血糖、调脂治疗等对症处理。在此基础上,对照组给予注射用地尔硫卓(天

津田边制药有限公司,国药准字J20160015,规格:10 mg) 40 mg溶于5%GS 100 mL或0.9%NS 100 mL治疗,按剂量2 μg/Kg/min微量泵入。研究组给予注射用地尔硫卓联合前列地尔注射液(哈药集团生物工程有限公司,国药准字H20084565规格:2 mL:10 μg)治疗,注射用地尔硫卓治疗方案同对照组,前列地尔注射液用法如下:将10 μg前列地尔注射液溶于100 mL氯化钠注射液中,静脉滴注。两组均连续治疗2周。

1.3 观察指标

(1)患者取左侧卧位,分别于治疗前、治疗2周后采用脉冲多普勒测量二尖瓣环舒张早期运动峰速度(E'),采用PHILIPS EPIQ7C彩色多普勒心脏超声诊断仪(探头频率2.5~3.0 MHz)检测两组心房收缩期二尖瓣口最大血流流速(A)、二尖瓣舒张早期血流峰速度(E),比较两组患者的E/A及E/E'。(2)考察两组治疗2周后的临床总有效率。按照美国纽约心脏功能分级(NYHA)制定疗效标准:显效:心功能提高不小于2级,症状或体征消失或显著改善。有效:心功能提高不小于1级,症状或体征有所改善。无效:症状、体征或心功能无明显改善甚至加重。总有效=显效+有效^[10]。(3)分别于治疗前、治疗2周后抽取患者晨起空腹肘静脉血6 mL,经离心处理后(3900 r/min离心12 min,离心半径8 cm)取血清样品保存待测。B型尿钠肽(BNP)采用放射免疫法检测,C反应蛋白(CRP)采用免疫比浊法检测,白细胞介素(IL)-6、巨噬细胞移动抑制因子(MIF)、鸟嘌呤(8-O-HdG)采用酶联免疫吸附法检测,超氧化物歧化酶(SOD)、丙二醛(MDA)采用分光光度法检测,所有试剂盒均采购自武汉博士德生物工程有限公司,严格按照试剂盒步骤进行。(4)记录不良反应。

1.4 统计学方法

SPSS 25.0 进行数据分析,计量资料符合正态分布,具备方差齐性以($\bar{x} \pm s$)表示,组间比较采用t检验。以率(%)表示计数资料采用 χ^2 检验。检验水准 $\alpha=0.05$ 。

2 结果

2.1 两组疗效比较

与对照组的总有效率75.93%(41/54)相比,研究组的总有效率92.59%(50/54)更高($P<0.05$),详见表1。

2.2 两组BNP、E/A、E/E'比较

两组BNP、E/A、E/E'治疗前比较无差异($P>0.05$),两组BNP、E/E'治疗2周后降低,E/A治疗2周后升高($P<0.05$),研究组治疗2周后BNP、E/E'低于对照组,E/A高于对照组($P<0.05$),详见表2。

2.3 两组炎症因子水平比较

两组IL-6、CRP、MIF治疗前比较无差异($P>0.05$),两组IL-6、CRP、MIF治疗2周后降低($P<0.05$),研究组治疗2周后IL-6、CRP、MIF低于对照组($P<0.05$),详见表3。

表 1 两组疗效比较例(%)

Table 1 Comparison of curative effects between the two groups n (%)

Groups	Obvious effect	Effective	Invalid	Total efficiency
Control group (n = 54)	14(25.93)	27(50.00)	13(24.07)	41(75.93)
Study group (n = 54)	19(35.19)	31(57.41)	4(7.41)	50(92.59)
χ^2				5.655
P				0.017

表 2 两组 BNP、E/A、E/E' 比较($\bar{x} \pm s$)Table 2 Comparison of BNP, E/A, E/E' between the two groups($\bar{x} \pm s$)

Groups	BNP(pg/mL)		E/A		E/E'	
	Before treatment	After 2 weeks of treatment	Before treatment	After 2 weeks of treatment	Before treatment	After 2 weeks of treatment
Control group (n=54)	3268.02± 292.64	2275.34± 154.59 ^a	0.92± 0.18	1.37± 0.22 ^a	11.03± 1.15	7.26± 1.35 ^a
Study group (n=54)	3257.45± 313.79	1349.37± 145.62 ^a	0.96± 0.21	1.82± 0.25 ^a	11.09± 1.07	5.07± 1.24 ^a
t	0.181	32.040	1.063	9.930	0.281	8.779
P	0.857	0.000	0.290	0.000	0.779	0.000

Note: Compared with before treatment, ^a $P < 0.05$.表 3 两组炎症因子水平比较($\bar{x} \pm s$)Table 3 Comparison of inflammatory factors between the two groups($\bar{x} \pm s$)

Groups	IL-6(pg/L)		CRP(mg/L)		MIF(pg/mL)	
	Before treatment	After 2 weeks of treatment	Before treatment	After 2 weeks of treatment	Before treatment	After 2 weeks of treatment
Control group (n=54)	624.25± 24.32	398.32± 32.61 ^a	44.65± 6.51	31.53± 5.21 ^a	326.24± 37.35	165.53± 19.21 ^a
Study group (n=54)	619.31± 23.41	286.52± 24.65 ^a	44.42± 7.42	20.15± 4.35 ^a	325.34± 40.37	113.99± 17.32 ^a
t	1.075	20.098	0.171	12.321	0.120	14.643
P	0.285	0.000	0.864	0.000	0.905	0.000

Note: Compared with before treatment, ^a $P < 0.05$.

2.4 两组氧化应激指标比较

($P < 0.05$), 研究组治疗 2 周后 8-OhdG、MDA 低于对照组, SOD

两组 8-OhdG、SOD、MDA 治疗前比较无差异($P > 0.05$), 两
组 8-OhdG、MDA 治疗 2 周后降低, SOD 治疗 2 周后升高

高于对照组($P < 0.05$), 详见表 4。表 4 两组氧化应激指标比较($\bar{x} \pm s$)Table 4 Comparison of oxidative stress indexes between the two groups($\bar{x} \pm s$)

Groups	8-OHdG(ng/mL)		SOD(μ g/mL)		MDA(mmol/L)	
	Before treatment	After 2 weeks of treatment	Before treatment	After 2 weeks of treatment	Before treatment	After 2 weeks of treatment
Control group (n=54)	4.15± 0.26	3.26± 0.37 ^a	62.32± 5.06	78.12± 6.35 ^a	8.34± 1.26	5.26± 1.86 ^a
Study group (n=54)	4.19± 0.38	2.15± 0.33 ^a	62.48± 7.01	94.01± 4.42 ^a	8.51± 1.34	3.05± 0.92 ^a
t	0.638	16.452	0.136	13.402	0.679	7.826
P	0.525	0.000	0.892	0.000	0.499	0.000

Note: Compared with before treatment, ^a $P < 0.05$.

2.5 不良反应

两组均未见明显不良反应发生。

当前我国的人口老龄化形式严峻, 心衰的发病率呈直线上
升趋势, 其中 HFpEF 在所有心衰患者中的发病率也越来越高,
且死亡率有所增加, 预后较差^[11]。HFpEF 的主要生理病理改变
为心室主动舒张动能障碍和心室顺应性下降导致的充盈障碍,

3 讨论

可能是因为钙离子无法被肌质网及时摄取进而泵出胞外,进而使心室主动舒张动能发生障碍^[12-14],在上述生理病理的作用下导致左室舒张末压明显升高,肺循环阻力升高,但因其收缩功能尚未受到明显影响,故而 LVEF 可维持基本正常^[15,16]。HFpEF 临床起病诱因多见,不少研究证实其发病与机体氧化应激反应失调有关^[17,18]。同时也有研究表明^[19],HFpEF 发病与血清中炎症反应长期处于高水平、机体微炎症水平持续增高有关。正是因为 HFpEF 临床发病机制的复杂性,致使其治疗至今尚无循证医学证据支持。地尔硫卓可通过降低钙超载进而松弛心室肌的主动舒张功能,从而使临床症状得以缓解^[20]。前列地尔是一种由花生四烯酸衍生的血管活性药物,由脂微球为药物载体而不易失活,在扩张血管、改善机体微循环等方面效果显著^[21]。既往动物模型及临床实践中均显示前列地尔在治疗心肌梗死、心绞痛以及心肌缺血-再灌注损伤等疾病中均有一定的保护作用^[22,23]。

本研究结果显示,与单用地尔硫卓治疗相比,联合前列地尔注射液能有效提升治疗效果,改善患者心功能。李倩等^[24]学者研究表明,地尔硫卓联合前列地尔注射液治疗 HFpEF,疗效明确,能显著改善患者心功能及生活质量。左室舒张功能弛豫主要影响左心室充盈,而 E/A、E/E' 是目前临床判断左心室充盈的主要指标,E/E' 比值越大,E/A 比值越低,提示患者左室舒张功能越差,BNP 则是判断舒张期心力衰竭的主要生物学指标,其水平越高,代表舒张期心力衰竭病情越严重。疗效提升原因可能与前列地尔可增强心肌收缩力、提高心排量,同时还可抑制钙离子游离,使外周阻力降低,血流动力学改善有关^[25]。氧化应激、炎症反应在 HFpEF 的病情进展中发挥重要作用,其相关指标水平检测可有效评估患者后续治疗效果。其中 IL-6 是体内常见的炎症因子,CRP 是体内常见的非特异性蛋白,均可反映心脑血管内皮细胞受损程度^[26]。MIF 是活化 T 淋巴细胞的产物,高表达的 MIF 可促进巨噬细胞趋化转移,使炎症介质大量释放,加剧体内炎症瀑布反应^[27]。8-OHdG、MDA、SOD 则均是反映机体氧化应激的常见指标,而氧化应激是促使心肌功能障碍的危险因素^[28]。本次研究结果中,注射用地尔硫卓联合前列地尔注射液可有效改善 IL-6、CRP、MIF、8-OHdG、MDA、SOD 等指标水平。提示该联合治疗可能是通过降低炎症反应,减轻氧化应激水平的机制来提高治疗效果。前列地尔发挥药效机制的主要在于改善血流动力学和调节神经内分泌两个方面,其一是通过有效的降低循环阻力,改善微循环。此外通过抑制体内某些神经体液因子的活化,进而抑制单核细胞、炎症细胞浸润及免疫复合物和抗体的形成,从而抑制细胞因子的活性和生成,减少炎症物质的释放,减轻氧化应激^[29,30]。此外,两组均未见明显不良反应发生,可见其安全性较好,患者耐受性高。本研究证实注射用地尔硫卓联合前列地尔注射液治疗 HFpEF 疗效理想,但样本含量仍较小,可能影响研究结论的稳定性,此外本次研究受时间限制未能观察中远期疗效,在未来的研究中尽可能收集更多的样本,增加随访观察,以获取更为准确的结果。

综上所述,注射用地尔硫卓联合前列地尔注射液能显著改善 HFpEF 患者心功能,改善机体血清炎症因子和氧化应激,安全有效。

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