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沙库巴曲缬沙坦联合胺碘酮对老年 HF 伴 PAF 患者心功能、炎症因子及神经内分泌激素的影响 *

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摘要 目的:探讨沙库巴曲缬沙坦联合胺碘酮对老年心力衰竭(HF)伴阵发性房颤(PAF)患者心功能、神经内分泌激素以及炎症因子的影响。**方法:**选取 2017 年 2 月~2019 年 1 月期间我院收治的 80 例老年 HF 伴 PAF 患者,根据随机数字表法分为研究组(n=40,沙库巴曲缬沙坦联合胺碘酮治疗)和对照组(n=40,胺碘酮治疗),比较两组患者疗效、心功能指标[左心室舒张末期内径(LVEDD)、左心室射血分数(LVEF)、左心室收缩末期内径(LVESD)],炎症因子[白介素-33(IL-33)、肿瘤坏死因子- α (TNF- α)、细胞间黏附分子-1(ICAM-1)]及神经内分泌激素(去甲肾上腺素、醛固酮和血管紧张素 II)水平及不良反应发生情况。**结果:**研究组治疗 3 个月后的临床总有效率 90.00%(36/40)高于对照组 67.50%(27/40)($P<0.05$)。两组治疗 3 个月后 LVEDD、ICAM-1、TNF- α 、LVESD、IL-33 均较治疗前降低,且研究组较对照组低($P<0.05$);LVEF 较治疗前提高,且研究组高于对照组($P<0.05$)。两组不良反应总发生率比较无差异($P>0.05$)。两组治疗 3 个月后去甲肾上腺素、醛固酮、血管紧张素 II 水平均较治疗前降低,且研究组低于对照组($P<0.05$)。**结论:**老年 HF 伴 PAF 患者在胺碘酮的基础上联合沙库巴曲缬沙坦治疗,心功能指标改善显著,血清炎症因子及神经内分泌激素水平有所降低,且安全可靠,疗效显著。

关键词:沙库巴曲缬沙坦;胺碘酮;老年;心力衰竭;阵发性房颤;心功能;炎症因子;神经内分泌激素

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Effects of Sakubatrevalsartan Combined with Amiodarone on Cardiac Function, Inflammatory Factors and Neuroendocrine Hormones in Elderly Patients with HF and PAF*

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ABSTRACT Objective: To investigate the effects of sakubatrevalsartan combined with amiodarone on cardiac function, inflammatory factors and neuroendocrine hormones in elderly patients with congestive heart failure (CHF) and paroxysmal atrial fibrillation (PAF). **Methods:** From February 2017 to January 2019, A total of 80 elderly patients with CHF and PAF who were admitted to our hospital were selected, they were divided into study group (n=40, sakubatrevalsartan combined with amiodarone) and control group (n=40, amiodarone) according to the random number table method. The efficacy and cardiac function indexes [left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), left ventricular end systolic diameter (LVESD)], inflammation factors [interleukin-33 (IL-33), tumor necrosis factor- α (TNF- α), intercellular adhesion molecule 1 (ICAM 1)] and neuroendocrine hormones (norepinephrine, aldosterone and angiotensin II) levels and adverse reactions occurred of the two groups were compared. **Results:** The total clinical effective rate of the study group after 3 months was 90.00%(36/40) higher than 67.50%(27/40) of the control group ($P<0.05$). 3 months after treatment, LVEDD, ICAM-1, TNF- α LVESD and IL-33 of the two groups were reduced compared with those before treatment, and the study group was lower than the control group ($P<0.05$). LVEF was higher than that before treatment, and the study group was higher than the control group ($P<0.05$). There was no significant difference in the total incidence of adverse reactions between the two groups ($P>0.05$). Norepinephrine, aldosterone and angiotensin II of the two groups at 3 months after treatment decreased compared with those before treatment, and study group was lower than control group ($P<0.05$). **Conclusion:** On the basis of amiodarone treatment, elderly patients with HF and PAF use the sakubatrevalsartan treat showed significant improvement in cardiac function indexes, decreased levels of serum inflammatory factors and neuroendocrine hormones, which are safe, reliable and effective.

Key words: Sakubatrevalsartan; Amiodarone; Old age; Heart failure; Paroxysmal atrial fibrillation; Cardiac function; Inflammatory factor; Neuroendocrine hormone

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前言

心力衰竭(Heart failure, HF)是各种心脏疾病的终末期阶段^[1]。而阵发性房颤(Paroxysmal atrial fibrillation, PAF)是指规则有序的心房电活动丧失,取而代之的是快速无序的颤动波^[2]。老年患者由于身体各项机能下降,且常合并多种基础性疾病,导致 HF 和 PAF 可同时发生^[3],并形成一种恶性循环,导致病情恶化。据以往资料统计^[4],约有 34.1%的老年 HF 患者可并发心房颤动,严重威胁患者生命健康。现临床有关老年 HF 伴 PAF 的治疗尚无统一方案,胺碘酮是一种抗心律失常药,临床常用于治疗 HF 合并心房颤动^[5],但长期应用副作用较大,效果难以达到预期。沙库巴曲缬沙坦是一种血管紧张素受体-脑啡肽酶抑制剂类心衰新药^[6],既往常用于高血压和 HF 的临床治疗中。本研究通过对我院收治的部分老年 HF 伴 PAF 患者给予沙库巴曲缬沙坦联合胺碘酮治疗,效果较好,报道如下。

1 资料与方法

1.1 一般资料

选取 2017 年 2 月~2019 年 1 月期间我院接收的老年 HF 伴 PAF 患者 80 例,纳入标准:(1)HF 参考《中国心力衰竭诊断和治疗指南(2014)》^[7],左心室射血分数(Left ventricular ejection fraction, LVEF) $\leq 45\%$;(2)PAF 诊断均符合《心电散点图及逆向技术对阵发性房颤的快速诊断》^[8]中的诊断标准;(3)均经心电图、胸片、超声心动图等检查确诊;(4)患者及其家属知情本研究且签署同意书;(5)美国纽约心脏病学会(New York Heart Association, NYHA)心功能分级为 II ~ IV 级;(6)年龄 ≥ 61 岁。排除标准:(1)合并恶性肿瘤者;(2)对本次研究用药存在障碍者;(3)合并肝肾等其他脏器严重功能障碍者;(4)合并病态窦房结综合征者;(5)既往有过心脏或胸部手术史;(6)合并急性脑出血或昏迷、休克、意识障碍者;(7)合并精神疾患,无法正常沟通交流者。根据随机数字表法分为研究组、对照组,其中对照组 40 例,男 21 例,女 19 例,合并房颤病程 2~9 月,平均 (4.36 ± 0.97) 月;年龄 61~82 岁,平均 (71.92 ± 3.16) 岁;心功能分级:II 级 17 例,III 级 14 例,IV 级 9 例;合并基础疾病:糖尿病 4 例,高血压 6 例,高血脂 8 例。研究组 40 例,男 23 例,女 17 例,合并房颤病程 2~11 月,平均 (4.52 ± 0.86) 月;年龄 61~80 岁,平均 (71.06 ± 4.06) 岁;心功能分级:II 级 18 例,III 级 16 例,IV 级 6 例;合并基础疾病:糖尿病 6 例,高血压 8 例,高血脂 9 例。两组一般资料对比无差异($P > 0.05$),均衡可比。此次研究已

通过我院医学伦理学委员会批准进行。

1.2 方法

两组均给予螺内酯片、地高辛片、抗凝、控制血糖、呋塞米片、利尿、吸氧、降压、调脂等基础治疗。在此基础上,对照组予以胺碘酮片 [赛诺菲(杭州)制药有限公司,国药准字 H19993254,规格:0.2 g] 治疗,口服,0.2 g/次,3 次/d;10 d 后改为 0.2 g/次,1 次/d;15 d 后改为 0.1 g/次,1 次/d,并维持此治疗方案至治疗结束。基于对照组治疗,研究组联合沙库巴曲缬沙坦 [Novartis Pharma Schweiz AG, 国药准字 J20190002,规格:沙库巴曲 49 mg/缬沙坦 51 mg] 治疗,初始剂量为 2 次/d,50 mg/次,随后视患者具体用药情况每 2 周倍增 1 次,2 次/d,最高 200 mg/次,维持此剂量,直至治疗结束。两组均治疗 3 个月。

1.3 观察指标

(1)记录两组总有效率。疗效判定标准如下^[9]:总有效 = 显效 + 有效。显效:静息心率 ≤ 80 次/min, NYHA 心功能改善 2 级及以上,患者主要症状、体征消失;有效:静息心率 81~89 次/min, NYHA 心功能改善 1 级,患者主要症状、体征有所改善;无效:症状、体征无改善甚至加重,静息心率 ≥ 90 次/min。(2)记录不良反应情况。(3)于治疗前、治疗 3 个月采用美国 Diasonics 公司生产的 Spectra 超声多普勒血流显像仪测量患者心功能指标:左心室舒张末期内径(Left ventricular end diastolic diameter, LVEDD)、LVEF 和左心室收缩末期内径(Left ventricular end systolic diameter, LVESD)。(4)于治疗前、治疗 3 个月后收集患者晨起外周肘静脉血 4 mL,及时送检,经充分离心(3800 r/min 离心 14 min,离心半径 13 cm),分离血清后,按照试剂盒(北京百泰克生物技术有限公司)说明书步骤,血浆神经内分泌激素(血管紧张素 II、醛固酮、去甲肾上腺素)水平采用放射免疫法检测。采用酶联免疫吸附试验检测血清炎症因子[白介素-33(IL-33)、肿瘤坏死因子- α (TNF- α)、细胞间黏附分子-1(ICAM-1)]水平。

1.4 统计学方法

研究数据经 SPSS25.0 软件处理,计量资料用($\bar{x} \pm s$)表示,行 t 检验,以例数及率表示计数资料,行 χ^2 检验, $\alpha = 0.05$ 为检验标准。

2 结果

2.1 两组疗效比较

研究组治疗 3 个月后的临床总有效率高干对照组($P < 0.05$);详见表 1。

表 1 两组总有效率比较 例(%)

Table 1 Comparison of total effective rate between two groups [n(%)]

Groups	Effective	Valid	Invalid	Total effective rate
Control group(n=40)	11(27.50)	16(40.00)	13(32.50)	27(67.50)
Study group(n=40)	15(37.50)	21(52.50)	4(10.00)	36(90.00)
χ^2				6.050
P				0.014

2.2 两组心功能指标比较

两组治疗前 LVEDD、LVEF、LVESD 比较无差异($P > 0.05$);

两组治疗 3 个月后 LVEDD、LVESD 均较治疗前缩小,且研究于对照组($P<0.05$);详见表 2。
组小于对照组($P<0.05$);LVEF 水平较治疗前升高,且研究组高

表 2 两组心功能指标比较($\bar{x} \pm s$)
Table 2 Comparison of cardiac function indexes between the two groups($\bar{x} \pm s$)

Groups	LVEF (%)		LVEDD(mm)		LVESD(mm)	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group (n=40)	37.58± 5.36	44.72± 4.49*	59.31± 5.13	53.47± 6.17*	43.74± 5.38	37.62± 4.82*
Study group(n=40)	37.17± 4.48	50.29± 4.69*	59.79± 6.38	46.42± 6.86*	43.29± 5.77	31.19± 4.73*
t	0.490	7.151	0.488	6.367	0.475	7.938
P	0.625	0.000	0.626	0.000	0.635	0.000

Note: compared with before treatment, * $P<0.05$.

2.3 两组炎症因子指标比较

两组患者治疗前 IL-33、TNF- α 、ICAM-1 水平比较差异无统计学意义 ($P>0.05$); 两组治疗 3 个月后 IL-33、TNF- α 、I-

CAM-1 水平均较治疗前降低,且研究组低于对照组($P<0.05$);

详见表 3。

表 3 两组炎症因子指标比较($\bar{x} \pm s$)
Table 3 Comparison of inflammatory factors between the two groups($\bar{x} \pm s$)

Groups	IL-33(ng/L)		TNF- α (ng/L)		ICAM-1(μ g/L)	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group(n=40)	253.29± 23.26	167.44± 23.11*	34.33± 4.26	25.01± 4.19*	652.86± 26.52	436.72± 28.37*
Study group(n=40)	252.11± 24.37	122.03± 25.68*	34.28± 5.29	16.73± 3.16*	651.05± 27.63	312.31± 26.21*
t	0.292	10.953	0.061	13.166	0.394	26.860
P	0.771	0.000	0.951	0.000	0.694	0.000

Note: compared with before treatment, * $P<0.05$.

2.4 两组神经内分泌激素比较

治疗前,两组去甲肾上腺素、醛固酮、血管紧张素 II 水平比较无差异($P>0.05$);治疗 3 个月后,两组去甲肾上腺素、醛固

酮、血管紧张素 II 水平均较治疗前降低,且研究组较对照组低($P<0.05$);详见表 4。

表 4 两组神经内分泌激素比较($\bar{x} \pm s$)
Table 4 Comparison of neuroendocrine hormones between the two groups($\bar{x} \pm s$)

Groups	Norepinephrine(pmol/L)		Aldosterone(ng/L)		Angiotensin II (ng/L)	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group(n=40)	2432.53± 162.17	1849.08± 141.29*	332.34± 45.92	287.62± 34.88*	123.34± 10.21	82.23± 15.34*
Study group(n=40)	2430.58± 158.16	1287.33± 138.25*	329.79± 56.89	243.78± 43.74*	122.29± 14.38	63.31± 12.18*
t	0.072	23.968	0.291	6.527	0.496	8.059
P	0.943	0.000	0.772	0.000	0.621	0.000

Note: compared with before treatment, * $P<0.05$.

2.5 两组不良反应比较

两组不良反应总发生率比较无差异($P>0.05$);详见表 5。

3 讨论

HF 是一种复杂的症候群,主要症状表现为呼吸困难、无力

等,可导致心脏结构和功能的改变,造成心脏泵血功能下降^[10-12]。心房颤动是指心脏的电活动紊乱,导致心房无法正常舒张及收缩,最终引起全身循环障碍的一类疾病^[13,14]。HF 患者由于 LVEF 处于较低水平,心电活动不稳,交感神经兴奋,可通过异位起搏细胞水平反常性增高、折返运动等诸多途径引发 PAF^[15]。HF 伴

表 5 两组不良反应比较 例(%)

Table 5 Comparison of adverse reactions between the two groups [n(%)]

Groups	Abnormal liver function	Sinus bradycardia	Nausea and vomiting	Gastrointestinal discomfort	Total incidence rate
Control group(n=40)	2(5.00)	2(5.00)	1(2.50)	2(5.00)	7(17.50)
Study group(n=40)	3(7.50)	2(5.00)	2(5.00)	3(7.50)	10(25.00)
χ^2					0.555
P					0.456

PAF 时,过快的心室反应,会诱发心动过速心肌病、心悸,使患者房室及窦房结功能下降,增加病死率;此外,房颤会失去心房辅助泵的作用,进而影响机体心功能^[6,7]。既往就有研究证实^[18],心房颤动是 HF 患者再住院和死亡的重要独立危险因素。现临床有关 HF 伴 PAF 的具体发病机制尚不十分明确,有学者认为心室重构在 HF 伴 PAF 发生和发展中发挥重要作用^[19]。而神经内分泌系统的过度激活会产生大量神经内分泌因子,在心室重塑的发展过程中发挥关键作用^[20]。长期血流动力学的改变,会使心脏容量负荷增加,导致细胞因子和信号肽的释放,或引起炎症应激,导致心室重塑。因此 HF 伴 PAF 的治疗目标不仅是改善症状,更重要的是抑制炎症系统、神经内分泌系统的过度激活,以降低 HF 伴 PAF 的住院率和死亡率^[21-23]。

本次研究结果显示,老年 HF 伴 PAF 患者在胺碘酮治疗的基础上联合沙库巴曲缬沙坦心功能改善确切,可有效提高治疗效果。胺碘酮作为目前唯一无明显负性肌力作用的广谱抗心律失常药物,可使窦房结频率降低,延长心室和心房肌动作电位时间、有效不应期,延长房室传导时间^[24,25]。此外,胺碘酮还可增加冠脉血流量,利于心肌缺血症状的改善。沙库巴曲缬沙坦钠片是由缬沙坦(血管紧张素 II 受体拮抗剂)以及沙库巴曲(脑啡肽酶抑制剂)组成的复方制剂,故该药物可发挥尿钠排泄、血管扩张以及通过阻断血管紧张素 II 发挥排钠利尿、降低机体醛固酮的释放等作用^[26]。此外,沙库巴曲缬沙坦还可选择性作用于心肌 L 型钙通道的失活态、心房肌细胞膜,延长心房动作电位时程,停止心房阻滞产生的不规则折返,有效抑制房颤反复发作^[27]。神经内分泌系统活性可以通过血浆醛固酮、去甲肾上腺素、血管紧张素 II 的浓度反映,去甲肾上腺素持续升高,导致血液动力学障碍,心脏负荷、能量消耗加重^[28];而短期升高的血管紧张素 II 以及醛固酮水平可维持组织灌注,但是长久的过度激活可导致血管压力增加,引起水钠潴留和循环血量增加,血管负荷加重,促使疾病进展。心室重塑的发生发展离不开炎症系统的激活,IL-33、TNF- α 、ICAM-1 作为临床常见的炎症因子,均参与着心肌细胞的炎症反应、坏死,心衰等过程^[29]。本研究中沙库巴曲缬沙坦联合胺碘酮治疗可有效降低炎症因子及神经内分泌激素水平。分析可能是因为沙库巴曲缬沙坦可阻断血管紧张素 II 介导的心房间质纤维化的信号转导通路,改善 HF 伴 PAF 发生时的血流动力学,延缓房颤心房结构重塑,进而抑制炎症系统、神经内分泌系统的激活^[30]。此外,本研究中两组不良反应总发生率比较无差异提示两药联合治疗安全可靠。

综上所述,老年 HF 伴 PAF 患者在胺碘酮的基础上联合沙库巴曲缬沙坦治疗,心功能指标改善显著,血清炎症因子及神

经内分泌激素水平有所降低,且安全可靠,疗效显著。

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