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沙库巴曲缬沙坦钠片对高原地区慢性心力衰竭患者神经内分泌激素和心功能的影响*

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摘要 目的:探讨沙库巴曲缬沙坦钠片治疗高原地区慢性心力衰竭(CHF)患者的疗效及对神经内分泌激素和心功能的影响。**方法:**选取2017年3月~2019年6月期间我院接收的CHF患者109例。根据随机数字表法将患者随机分为对照组(n=54)和研究组(n=55),对照组患者予以缬沙坦治疗,研究组患者则予以沙库巴曲缬沙坦钠片治疗,比较两组患者疗效、神经内分泌激素指标[去甲肾上腺素(NA)、醛固酮(ALD)、血管紧张素II(Ang II)]和心功能指标[超敏心肌肌钙蛋白T(hs-cTnT)、N-末端脑钠肽前体(NT-proBNP)、左房内径(LAD)、左室舒张末期径(LVEDD)以及左室射血分数(LVEF)]。记录两组患者心血管不良事件发生情况。**结果:**研究组患者治疗12周后总有效率为90.91%(50/55),显著高于对照组患者的75.93%(41/54)($P<0.05$)。两组治疗12周后ALD、NA、Ang II均下降,且研究组低于对照组($P<0.05$)。两组治疗12周后hs-cTnT、NT-proBNP、LVEDD、LAD均下降,且研究组低于对照组($P<0.05$);LVEF升高,且研究组高于对照组($P<0.05$)。两组心血管不良事件发生率对比无差异($P>0.05$)。**结论:**沙库巴曲缬沙坦钠片治疗高原地区CHF患者,疗效显著,可有效改善神经内分泌激素水平和心功能,且不增加心血管不良事件发生率,临床应用价值较高。

关键词:沙库巴曲缬沙坦钠片;高原地区;慢性心力衰竭;疗效;神经内分泌激素;心功能

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Effect of Sacubatrovalsartan Sodium Tablet on Neuroendocrine Hormones and Cardiac Function in Patients with Chronic Heart Failure at High Altitude*

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ABSTRACT Objective: To investigate the effect of sacubatrovalsartan sodium in the treatment of chronic heart failure (CHF) at high altitude and its influence on neuroendocrine hormone and cardiac function. **Methods:** From March 2017 to June 2019, 109 patients with CHF who were admitted to our hospital were selected. Patients were randomly divided into control group (n=54) and study group (n=55) according to the method of random number table. Patients in the control group were treated with valsartan, while patients in the study group were treated with sodium sakubatrovalsartan. The curative effect, neuroendocrine hormone indexes [(norepinephrine (NA), aldosterone (ALD), angiotensin II (Ang II)] and cardiac function indexes [high sensitivity cardiac troponin T (hs-cTnT), N-terminal pro brain natriuretic peptide (NT-proBNP), left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF)] were compared between the two groups. The incidence of cardiovascular adverse events of the two groups was recorded. **Results:** The total effective rate of the study group was 90.91%(50/55) at 12 weeks after treatment, which was significantly higher than 75.93% (41/54) of the control group ($P<0.05$). 12 weeks after treatment, ALD, NA, Ang II decreased in the two groups, and those of the study group were lower than those of the control group($P<0.05$). 12 weeks after treatment, hs-cTnT, NT-proBNP, LVEDD and LAD were all decreased of the two groups, and those of the study group were lower than those of the control group ($P<0.05$). The LVEF increased, and that of the study group was higher than that of the control group ($P<0.05$). There was no difference in the incidence of cardiovascular adverse events between the two groups($P>0.05$). **Conclusion:** Sacubatrovalsartan sodium is effective in the treatment of CHF at high altitude. It can effectively improve the neuroendocrine hormone and cardiac function without increasing the incidence of adverse events. It has a high clinical application value.

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Key words: Sacubatrovalsartan sodium tablets; High altitude; Chronic heart failure; Efficacy; Neuroendocrine hormone; Heart function**Chinese Library Classification(CLC):** R541.61 **Document code:** A**Article ID:** 1673-6273(2021)12-2350-04

前言

慢性心力衰竭(Chronic heart failure, CHF)是指因各种原因引起的心脏结构和功能变化,导致心室泵血的临床综合征,是各类心脏疾病的终末阶段^[1-3]。高原地区空气稀薄,氧气压低,这种特殊的气候特点、地理环境对常住人群的生理功能产生不良影响,使得高原地区 CHF 患者病情极易反复发作^[4,5]。目前临床针对 CHF 的治疗尚无统一方案,多以阻止疾病进展、改善临床症状为主^[6]。缬沙坦是一种血管紧张素 II 受体 (Angiotensin II receptor, Ang II receptor)拮抗药,既往常用于 CHF 的治疗中^[7],但仍存在疗效一般,患者长期用药不良反应较大、依从性较差等不足。沙库巴曲缬沙坦钠片是新型双效神经激素调节剂,已被美国纽约心脏病协会(New York Heart Association, NYHA)、欧洲心脏病学会(European Society of Cardiology, ESC)所推荐^[8]。现临床有关沙库巴曲缬沙坦钠片治疗高原地区 CHF 患者的相关报道尚不多见,本研究就此展开分析,以期临床治疗高原地区 CHF 提供参考。

1 资料与方法

1.1 一般资料

选取 2017 年 3 月~2019 年 6 月期间我院接收的 CHF 患者 109 例。纳入标准:(1)诊断标准参考《2016 ESC 急性和慢性心力衰竭诊断和治疗指南》^[9],临床症状主要表现为阵发性呼吸困难、踝部水肿、肺水肿、心动过速等;(2)NYHA 分级 II~IV 级,左心室射血分数(Left ventricular ejection fraction, LVEF)≤40%^[10];(3)患者及其家属知情本研究且签署同意书;(4)均为高原地区常住人口。排除标准:(1)入院前 1 个月已接受过相关治疗者;(2)合并恶性肿瘤、免疫缺陷类疾病者;(3)合并其他心脏疾病导致的心功能不全者;(4)合并严重肝肾功能障碍者;(5)对本次研究使用药物存在过敏反应或禁忌症者;(6)伴有心源性休克者。本次研究已获取我院伦理学委员会批准进行。根据随机数字表法将患者随机分为对照组(n=54)和研究组(n=55),其中对照组男 31 例,女 23 例,年龄 52~73 岁,平均(63.42±3.95)岁;病程 1~6 年,平均(3.52±0.82)年;体质量指数 21.3~26.8 kg/m²,平均(23.51±0.97)kg/m²;NYHA 分级 II 级 29 例,III-IV 级 25 例。研究组男 33 例,女 22 例,年龄 53~74 岁,平均(62.98±3.74)岁;病程 2~8 年,平均(3.76±0.74)年;体质量指数 21.8~27.2 kg/m²,平均(23.36±1.22)kg/m²;NYHA 分级 II

级 32 例,III-IV 级 23 例。两组临床资料比较无差异($P>0.05$)。

1.2 治疗方法

两组患者均指导其正常作息,给予洋地黄类、 β -受体阻滞剂及利尿剂等药物进行基础治疗,同时嘱患者戒烟、戒酒,适量运动。在此基础上,对照组给予缬沙坦[浙江华海药业股份有限公司,国药准字 H20183126,规格:以缬沙坦($C_{24}H_{29}N_5O_3$)计 80 mg]治疗,80 mg/次,2 次/d。研究组则给予沙库巴曲缬沙坦钠片[Novartis Singapore Pharmaceutical Manufacturing Private.Ltd., 国药准字 J20190002,规格:以沙库巴曲缬沙坦计 100 mg(沙库巴曲 49 mg/缬沙坦 51 mg)]治疗,50 mg/次,2 次/d,如能耐受则于 2 周后调整为 100 mg/次,2 次/d。两组均连续治疗 12 周。

1.3 观察指标

(1)临床疗效:比较两组患者治疗 12 周后临床疗效。疗效判定标准如下^[9]:心功能改善≥2 级或恢复正常,临床症状改善(显效);心功能改善 1 级,临床症状改善(有效);心功能无变化甚至临床症状加重(无效);总有效率=显效率+有效率。(2)于治疗前、治疗 12 周后抽取患者清晨空腹静脉血 5 mL,经常规离心处理(3900 r/min 离心 12 min,离心半径 15 cm),分离上清液,置于冰箱(-30℃)中待测。采用放射免疫法检测去甲肾上腺素(Norepinephrine, NA)、醛固酮(Aldosterone, ALD)、血管紧张素 II (Angiotension II, Ang II)水平、超敏心肌肌钙蛋白 T(High sensitivity cardiac troponin T, hs-cTnT)、N-末端脑钠肽前体(N-terminal pro brain natriuretic peptide, NT-proBNP)水平,严格按照试剂盒(深圳市博卡生物技术有限公司)说明书步骤进行检测。(3)采用美国西门子公司 Sequoia512 心脏彩色多普勒超声诊断系统测量所有患者的左房内径(Left atrial diameter, LAD)、左室舒张末期内径(Left ventricular end diastolic diameter, LVEDD)以及 LVEF。(4)记录两组患者心源性死亡、因心力衰竭再入院等心血管不良事件。

1.4 统计学方法

研究数据录入 SPSS23.0 软件处理,用($\bar{x} \pm s$)表示计量资料,采用 t 检验,计数资料以率(%)表示,采用 χ^2 检验,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 临床疗效比较

研究组患者治疗 12 周后总有效率为 90.91%(50/55),显著高于对照组患者 75.93%(41/54)($P<0.05$),见表 1。

表 1 临床疗效比较 [例(%)]

Table 1 Comparison of clinical efficacy [n(%)]

Groups	Markedly effective	Valid	Invalid	Total effective rate
Control group(n=54)	15(27.78)	26(48.15)	13(24.07)	41(75.93)
Study group(n=55)	21(38.18)	29(52.73)	5(9.09)	50(90.91)
χ^2				4.448
P				0.035

2.2 两组神经内分泌激素比较 (P>0.05); 两组治疗 12 周后 ALD、NA、Ang II 均下降, 且研究
两组患者治疗前 ALD、NA、Ang II 比较差异无统计学意义 组较对照组降低 (P<0.05); 见表 2。

表 2 两组神经内分泌激素比较($\bar{x} \pm s$)

Table 2 Comparison of neuroendocrine hormones between the two groups($\bar{x} \pm s$)

Groups	ALD(ng/L)		NA(pmol/L)		Ang II (ng/L)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group(n=54)	304.16± 24.23	277.17± 26.15*	2257.85± 96.31	1952.09± 183.94*	118.03± 24.16	97.47± 18.62*
Study group(n=55)	302.56± 23.65	219.23± 23.04*	2238.24± 85.57	1542.98± 173.87*	116.69± 25.67	71.28± 16.51*
t	0.349	12.280	1.126	11.935	0.281	7.773
P	0.728	0.000	0.263	0.000	0.780	0.000

Note: comparison with before treatment, *P<0.05.

2.3 心功能相关指标比较 治疗 12 周后两组 LVEDD、LAD 均下降, 且研究组低于对照组
治疗前两组患者 LVEDD、LVEF、LAD 比较无差异(P>0.05); (P<0.05); LVEF 升高, 且研究组高于对照组(P<0.05), 见表 3。

表 3 两组 LVEDD、LAD、LVEF 比较($\bar{x} \pm s$)

Table 3 Comparison of LVEDD, LAD and LVEF between two groups($\bar{x} \pm s$)

Groups	LAD(mm)		LVEDD(mm)		LVEF(%)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group(n=54)	48.26± 3.71	44.16± 4.27*	67.58± 7.83	60.26± 5.26*	29.18± 3.27	36.71± 2.96*
Study group(n=55)	47.95± 4.08	39.86± 3.76*	67.25± 6.36	55.28± 4.82*	29.46± 3.32	44.72± 3.02*
t	0.415	5.583	0.242	5.155	0.444	13.982
P	0.679	0.000	0.809	0.000	0.658	0.000

Note: comparison with before treatment, *P<0.05.

2.4 两组 hs-cTnT、NT-proBNP 比较 意义(P>0.05); 两组治疗 12 周后 hs-cTnT、NT-proBNP 均下降,
两组患者治疗前 hs-cTnT、NT-proBNP 比较差异无统计学 且研究组低于对照组 (P<0.05); 见表 4。

表 4 两组 hs-cTnT、NT-proBNP 比较($\bar{x} \pm s$)

Table 4 Comparison of hs-cTnT and NT-proBNP between two groups($\bar{x} \pm s$)

Groups	hs-cTnT(pg/mL)		NT-proBNP(pg/mL)	
	Before treatment	12 weeks after treatment	Before treatment	12 weeks after treatment
Control group(n=54)	29.21± 3.59	24.15± 3.52*	8814.16± 252.63	3529.98± 181.62*
Study group(n=55)	29.07± 4.61	19.03± 2.54*	8783.89± 231.69	2276.06± 294.37*
t	0.177	8.720	0.652	48.029
P	0.860	0.000	0.516	0.000

Note: comparison with before treatment, *P<0.05.

2.5 两组心血管不良事件发生率比较

对照组出现 3 例心源性死亡、3 例因心力衰竭再入院, 心血管不良事件发生率为 11.11%(6/54); 研究组出现 1 例心源性死亡、2 例因心力衰竭再入院, 心血管不良事件发生率为 5.45%(3/55); 两组不良事件发生率对比无差异($\chi^2=1.159$, $P=0.283$)。

3 讨论

CHF 具有发病率高、致死率高的特点, 近年来, 随着我国冠

心病、高血压等疾病患病率的提高及人口老龄化的加剧, 我国 CHF 的患病率也逐渐升高, 给社会带来了沉重的负担^[11-13]。高原有不同于平原的地理环境, 其中高原气候对长期生长、生活和工作在高原地区的人们的身体健康有着持久而直接的影响。生活在高原地区的人们长期处于一定程度的低氧状态下, 其 CHF 发病率及治疗后的不良事件发生率均高于生活在平原地区的人群, 加之部分高原地区医疗条件较差, 部分患者就诊时临床症状较重却不能得到比较有效的治疗, 因此心脏调节功能受到

严重损伤,影响机体内循环,加重组织损伤^[14]。在 CHF 的发病过程中,肾素-血管紧张素系统的活化发挥着重要作用,长期的肾素-血管紧张素系统的活化,可导致心室重塑,并降低血管内皮细胞分泌一氧化氮的能力,影响血管舒张,同时还可激活神经内分泌激素,从多个机制出发增加心脏负荷,加重心功能恶化^[15-17]。缬沙坦是经典的 CHF 治疗药物,可在一定程度改善患者预后,但仍未能达到预期效果^[18,19]。沙库巴曲缬沙坦钠片是脑啡肽酶抑制剂(沙库巴曲)与血管紧张素受体阻滞剂(缬沙坦)的复合物,两种药物相互协同作用使治疗 CHF 有了新的进展^[20,21]。但有关其用于高原地区 CHF 患者的具体疗效尚需进一步的实验以证实。

本次研究显示,治疗 12 周后研究组总有效率较对照组高,可见沙库巴曲缬沙坦钠片治疗高原地区 CHF 患者,可进一步提高治疗效果。分析其原因,缬沙坦通过抑制肾素-血管紧张素-醛固酮系统,发挥减少水钠潴留、减轻心脏负荷及舒张血管的作用;而沙库巴曲则可通过抑制脑啡肽酶的活性而增强利钠肽的有益作用,进而发挥其扩张血管、排钠利尿的作用;两种药物从不同的作用机制出发,发挥协同作用,共同提高治疗效果^[22-24]。现临床普遍认为心室重构是 CHF 发生和发展的主要机制,而神经内分泌系统的过度激活会产生大量 ALD、NA、Ang II 等神经内分泌因子,上述因子则在心室重构的发展过程中发挥关键作用^[25]。本研究中两组患者 ALD、NA、Ang II 均有所下降,且沙库巴曲缬沙坦钠片治疗者降低效果更为显著。究其原因,缬沙坦可阻断 Ang II 的 I 型受体,而沙库巴曲是一种前体药物,进入人体后可抑制脑啡肽酶,减少脑钠肽降解^[26,27]。两种作用通路均可抵抗神经内分泌过度激活,抑制 ALD、NA、Ang II 的释放。本次研究结果还显示,研究组的 hs-cTnT、NT-proBNP、LVEDD、LAD、LVEF 改善效果均优于对照组,其中 hs-cTnT 是心肌细胞特有的蛋白,因其灵敏度、特异度更高,已成为心肌损伤诊断的金标准,且与心肌损伤程度呈正相关^[28]。NT-proBNP 是一种主要由心室肌受到牵拉后分泌的肽类激素,可用于评估 CHF 患者病情及预后^[29]。LVEDD、LAD、LVEF 是临床评价患者心功能的常见指标。研究组心功能改善效果更佳原因可能在于脑啡肽酶是利钠肽降解的关键酶,分布广泛,通过沙库巴曲抑制脑啡肽酶对利钠肽的降解作用,升高利钠肽水平,进一步抑制心肌重构,改善机体心功能状况^[30]。另两组心血管不良事件发生率对比无差异,可见沙库巴曲缬沙坦钠片治疗 CHF 用药安全性较好。

综上所述,沙库巴曲缬沙坦钠片治疗高原地区 CHF 患者,疗效显著,可有效改善神经内分泌激素水平和心功能,且心血管不良事件发生率较低。

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