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沙库巴曲缬沙坦联合美托洛尔治疗老年慢性心功能不全的临床效果 *

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摘要 目的：研究沙库巴曲缬沙坦联合美托洛尔治疗老年慢性心功能不全的临床效果及安全性。**方法：**选择 2018 年 1 月～2019 年 1 月我院收治的 82 例老年慢性心功能不全患者并将其随机分为两组。对照组患者在常规治疗的基础上口服美托洛尔治疗，每次 25 mg，每天 2 次；观察组在对照组的基础上联合口服沙库巴曲缬沙坦，初始的给药剂量为每次 50 mg，每天 2 次，然后每 2 周增加 50 mg，最高给药剂量为每次 200 mg。比较两组治疗前后的左室射血分数(LVEF)、生存质量表(KCCQ)评分、6 min 步行距离、血清细胞间黏附分子 -1(ICAM-1)、N 端 B 型脑钠肽(NT-pro BNP)以及醛固酮(ALD)水平的变化及治疗期间不良反应的发生情况。**结果：**治疗后，观察组的有效率明显高于对照组(90.24% vs. 73.17%，*P*<0.05)；两组的 LVEF、6 min 步行距离和 KCCQ 评分均较治疗前明显升高，血清 ICAM-1、NT-pro BNP 以及 ALD 水平均较治疗前明显降低，且上述指标观察组变化更显著(均 *P*<0.05)。两组治疗期间心动过缓，头晕、头痛，高钾血症，低血压和肝肾功能异常的发生率比较差异无明显统计学意义(*P*>0.05)。**结论：**与单用美托洛尔治疗相比，沙库巴曲缬沙坦联合美托洛尔能更有效改善老年慢性心功能不全患者的心功能及生活质量，且安全性较高。

关键词：美托洛尔；沙库巴曲缬沙坦；老年慢性心功能不全

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Clinical Efficacy of Sakubatril Valsartan Combined with Metoprolol in the Treatment of Elderly Patients with Chronic Cardiac Insufficiency*

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ABSTRACT Objective: To study the clinical effect and safety of sakubatril valsartan combined with metoprolol in the treatment of elderly patients with chronic cardiac insufficiency. **Methods:** 82 elderly patients with chronic cardiac insufficiency who were treated in our hospital from January 2018 to January 2019 were randomly divided into two groups. The control group was treated with metoprolol only, 25 mg each time, twice a day. The observation group was with oral shakuba valsartan on the basis of the control group, the initial dosage was 50 mg each time, twice a day, and then increased by 50 mg every two weeks, the highest dosage was 200 mg each time. The changes of LVEF, KCCQ score and 6-minute walking distance, ICAM-1, NT-pro BNP and ALD before and after treatment, and the occurrence of adverse reactions during treatment were compared between the two group. **Results:** After treatment, the effective rate of observation group was significantly higher than that of the control group (90.24% vs. 73.17%, *P*<0.05), the LVEF, 6-minute walking distance and KCCQ scores of the two groups were significantly higher, and the serum ICAM-1, NT-pro BNP and ALD levels were significantly lower, the above index in the observation group improved better than those of te control group(both *P*<0.05). There was no significant difference in the incidence of bradycardia, dizziness, headache, hyperkalemia, hypotension and hepatorenal dysfunction during the two groups(*P*>0.05). **Conclusion:** Compared with metoprolol alone, sirolimus combined with metoprolol is more effective and safe in improving the cardiac function and the quality of life in elderly patients with chronic cardiac insufficiency.

Key words: Metoprolol; Sakubatril and valsartan; Chronic heart failure in the elderly

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前言

慢性心功能不全是各种终末期心脏疾病最为常见的一种临床表现，是心血管疾病患者的主要死亡原因[1,2]。慢性心功能

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不全主要的器质性病变为收缩及舒张功能出现障碍，心脏的泵血量不足，大约一半以上的患者由于发生心律失常而死亡，尤其是室性心动过速或心室颤动，能使病情趋于恶化，对患者产生巨大的健康威胁[3-5]。慢性心功能不全的临床表现包括咳嗽咳痰、心慌、呼吸困难以及双下肢水肿等[6]，发生机制是由于交感神经系统被激活，心肌受到损伤或心脏负荷过重，导致心脏衰竭[7-9]。该种疾病目前主要采取多种药物联用治疗，但最佳的治疗方案仍然处于探索过程中。

美托洛尔具有抑制交感神经系统过度激活的临床效果，可明显减少增殖因子的分泌，进而对血管及心脏的重构发挥抑制作用[10,11]。沙库巴曲缬沙坦钠能有效拮抗血管紧张素受体，且明显抑制脑啡肽酶。为了进一步探寻出更加有效且安全的治疗对策和治疗药物，本研究将沙库巴曲缬沙坦以及美托洛尔联合使用，分析了其对于老年慢性心功能不全的疗效及安全性。

1 临床资料

1.1 一般资料

选择 2018 年 1 月～2019 年 1 月我院收治的 82 例老年慢性心功能不全患者，纳入标准：依据临床病症、病史、心脏 B 超以及 X 线片等临床辅助检查确诊为慢性心功能不全，知情同意，心功能属于Ⅱ级～Ⅳ级。排除标准：对沙库巴曲缬沙坦以及美托洛尔过敏者，窦性心动过缓、Ⅱ～Ⅲ度房室传导阻滞、慢性阻塞性肺病、支气管哮喘、低血压和肝肾功能不全，不是首次患病的慢性心功能不全患者。用抽签法随机分为两组。观察组 41 例，男 23 例，女 18 例；年龄 60～87 岁，平均 (69.34± 7.83) 岁；其中，心功能Ⅱ级病人 19 例，Ⅲ级病人 10 例，Ⅳ级病人 12 例；高血压性心脏病 15 例，风湿性心脏病 16 例，缺血性心脏病 10 例。对照组 41 例，男 22 例，女 19 例；年龄 60～86 岁，平均 (69.76± 8.34) 岁；其中，心功能Ⅱ级病人 18 例，Ⅲ级病人 10 例，Ⅳ级病人 13 例；高血压性心脏病 16 例，风湿性心脏病 15 例，缺血性心脏病 10 例。两组的基线资料具有可比性。

1.2 治疗方法

两组均采取常规内科治疗，去除诱因，利尿、强心、扩冠治疗，并且注意休息，控制盐的摄入，吸氧。对照组：只口服美托洛尔治疗，每次 25 mg，每天 2 次；观察组：在口服美托洛尔的基础上，联合口服沙库巴曲缬沙坦，初始的给药剂量为每次 50 mg，每天 2 次，然后每 2 周增加 50 mg，最高给药剂量为每次 200 mg。两组的疗程均为 2 个月。

1.3 观察指标

比较两组治疗后 3 个月的疗效：① 显效：患者的心脏功能提高≥ 2 级，慢性心功能不全相关的症状大致消失；② 有效：患者的心脏功能提高 1 级，慢性心功能不全相关的症状有所改善；③ 无效：心脏功能无改善甚至恶化。

在治疗前后，采用美国 ATL 公司 APOGEE800 型超声心动仪检测 LVEF，并且测量患者的 6 min 步行距离；采取心肌病患者生存质量表(KCCQ)判断两组的生活质量改变情况，KCCQ 量表总共包括 5 个维度以及 23 个条目，总分 100 分，分值越低，生活质量越差；采取 ELISA 法检测两组的血清 ICAM-1、NT-pro BNP 以及 ALD 水平，试剂盒购自上海邦奕生物公司。

记录患者心动过缓，头晕、头痛，高钾血症，低血压和肝肾功能异常的发生情况。

1.4 统计学分析

采用 SPSS22.0，两组间计量资料对比用 t 检验，计数资料用 x^2 检验，P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后，观察组的有效率为 90.24%，明显高于对照组 (73,17%，P<0.05)，见表 1。

表 1 两组临床疗效比较 [例(%)]

Table 1 Comparison of the clinical effect between the two groups [n (%)]

Groups	n	Effective	Valid	Invalid	Total effect rate
Control group	41	16(39.02)	14(34.15)	11(26.83)	73.17
Observation group	41	21(51.22)	16(39.02)	4(9.76)	90.24*

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

2.2 两组治疗前后 LVEF、6 min 步行距离和 KCCQ 评分比较

治疗后，两组的 LVEF、6 min 步行距离和 KCCQ 评分均较治疗前明显升高(P<0.05)，且观察组的 LVEF、6 min 步行距离和 KCCQ 评分明显高于对照组(P<0.05)，见表 2。

表 2 两组治疗前后的 LVEF、6 min 步行距离和 KCCQ 评分比较($\bar{x}\pm s$)

Table 2 Comparison of the serum ICAM-1, NT-pro BNP and ALD levels before and after treatment between the two groups($\bar{x}\pm s$)

Groups	n		LVEF(%)	6-minute walking distance(m)	KCCQ score(point)
Control group	41	Before treatment	33.72± 4.96	197.47± 53.82	57.39± 10.24
		After treatment	41.28± 5.34#	264.5362.57#	69.44± 12.36
Observation group	41	Before treatment	34.19± 4.32	198.36± 54.21	58.26± 11.39
		After treatment	49.37± 6.24*#	342.5873.41*#	81.3± 15.42*#

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

2.3 两组治疗前后血清 ICAM-1、NT-pro BNP 以及 ALD 水平的比较

治疗后，两组的血清 ICAM-1、NT-pro BNP 以及 ALD 水平均较治疗前明显降低（$P<0.05$），且观察组的血清 ICAM-1、NT-pro BNP 以及 ALD 水平明显低于对照组($P<0.05$)，见表 3。

表 3 两组治疗前后的血清 ICAM-1、NT-pro BNP 以及 ALD 水平比较($\bar{x}\pm s$)

Table 3 Comparison of the LVEF, 6-minute walking distance and KCCQ score before and after treatment between the two groups($\bar{x}\pm s$)

Groups	n		ICAM-1(ng/L)	NT-pro BNP(pg/mL)	ALD (pg/mL)
Control group	41	Before treatment	64.39± 4.72	691.72± 54.38	232.7± 32.46
		After treatment	45.14± 3.92#	526.4± 48.57#	192.4± 26.53#
Observation group	41	Before treatment	65.87± 4.36	692.58± 55.24	233.5± 33.89
		After treatment	33.62± 3.54*#	413.29± 40.62*#	163.57± 22.38*#

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

2.4 两组治疗期间不良反应的发生情况

两组心动过缓，头晕、头痛，高钾血症，低血压和肝肾功能异常的发生率比较差异无明显统计学意义($P>0.05$)，见表 4。

表 4 两组不良反应发生情况的比较 [例(%)]

Table 4 Comparison of the incidence of adverse reactions between the two groups [n (%)]

Groups	n	Bradycardia	Dizziness	Headache	Hyperkalemia	Hypotension	Liver And Kidney Dysfunction	The total rate
Control group	41	1(2.44)	1(2.44)	1(2.44)	1(2.44)	1(2.44)	0(0.00)	12.19
Observation group	41	1(2.44)	1(2.44)	1(2.44)	0(0.00)	1(2.44)	0(0.00)	9.76

3 讨论

慢性心功能不全是因为心肌病、心肌梗死、炎症反应和血流动力学负荷过重等原因使心肌受到损伤，心肌的功能及结构发生改变，导致心室充盈或者泵血功能降低[12-15]。慢性心功能不全患者主要表现为心脏的排血量降低、心慌、咳嗽咳痰、双下肢发生充盈或者浮肿、颈静脉怒张和呼吸困难等，心脏、肾脏的功能以及体内电解质的异常及心肌的重建是慢性心功能不全主要的生理学改变[16-18]。目前，慢性心功能不全的治疗已由以往的强心、扩血管和利尿等短期控制方法转变成以修复神经内分泌抑制剂的长期疗法为主[19-21]。

沙库巴曲缬沙坦具有双靶点调节作用，一方面，其可以通过该药中的脑啡肽酶抑制剂，使 NT-pro BNP 的降解受到进一步的抑制，明显提高环磷鸟嘌呤核苷水平，从而有效缓解病情；另一方面，其能明显抑制血管紧张素Ⅱ受体拮抗剂的 1 型受体，有效激活 RAS[22-24]。本研究结果显示在美托洛尔的基础上，联用沙库巴曲缬沙坦能提高老年慢性心功能不全患者的疗效。分析其与原因可能在于：一方面，沙库巴曲缬沙坦中的脑啡肽酶抑制剂可以明显提高利钠肽水平，促进患者机体钠尿排泄速度的加快，同时可以有效促进血管舒张，抑制心室重构及交感神经的活性；另一方面，沙库巴曲缬沙坦中的缬沙坦以及沙库巴曲这两种成分通过口服给药后，能产生 LBQ657，使得该药能在服药之后的 1.5~4.5 h 达到血药浓度峰值，而且可以在服药 3 d 后在患者的机体中维持平稳的血药浓度，与单独服用缬沙坦相比较，沙库巴曲缬沙坦的生物利用度更好[25-27]。

ICAM-1 可促进血小板细胞、炎症细胞以及内皮细胞黏附，引发血栓形成，促进心肌缺血[28-30]。NT-pro BNP 目前主要用于慢性心功能不全的诊断、预后评估和治疗效果监测[31]。ALD 在机体中具有相对较短的半衰期和比较高的代谢清除率，对慢性心功能不全的鉴别诊断具有一定的应用价值[32]。本研究中，观察组治疗后的血清 ICAM-1、NT-pro BNP 以及 ALD 水平明显低于对照组，表明沙库巴曲缬沙坦联合美托洛尔能改善老年慢性心功能不全。此外，两组心动过缓、头晕、头痛、高钾血症、低血压和肝肾功能异常的发生率无明显差异，表明沙库巴曲缬沙坦具有较高的安全性。但本研究的病例偏少，未对治疗后 1 个月、6 个月及更长时间的治效果进行评估，后续仍需选取大样本进行更深入地研究。

综上所述，与单用美托洛尔治疗相比，沙库巴曲缬沙坦联合美托洛尔能更有效改善老年慢性心功能不全患者的心功能及生活质量，且安全性较高。

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