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托伐普坦联合氢氯噻嗪治疗慢性心力衰竭的疗效及对血清 Hcy、NTpro-BNP 水平的影响 *

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摘要 目的: 探讨托伐普坦联合氢氯噻嗪治疗慢性心力衰竭的疗效及对患者血清同型半胱氨酸 (Hcy)、N 末端脑钠肽前体 (NTpro-BNP) 水平的影响。方法: 选择 2018 年 1 月-2019 年 12 月在我院接受治疗的 94 例慢性心力衰竭患者, 采用抽签法分为观察组 (n=47) 和对照组 (n=47)。对照组给予氢氯噻嗪治疗, 观察组在对照组的基础上给予托伐普坦治疗。比较两组患者的临床疗效、治疗前后血清 Hcy、NTpro-BNP、左室收缩末期内径 (LVESD)、左心室射血分数 (LVEF)、6min 步行距离、层粘连蛋白 (LN)、透明质酸 (HA) 水平的变化情况及不良反应发生情况。结果: 治疗后, 两组总有效率分别为 93.62%, 74.47%, 观察组显著高于对照组 ($P<0.05$); 治疗前, 两组血清 Hcy、NTpro-BNP 水平比较无明显差异; 治疗后, 两组血清 Hcy、NTpro-BNP 水平均较治疗前显著降低, 且观察组上述指标均明显低于对照组 ($P<0.05$); 治疗前, 两组 LVESD、LVEF、6min 步行距离水平无明显差异; 治疗后, 两组 LVEF、6 min 步行距离水平均较治疗前显著升高, 且观察组高于对照组, 两组 LVESD 水平较治疗前显著下降, 且观察组显著低于对照组 ($P<0.05$); 治疗前, 两组心肌纤维化指标水平无明显差异; 治疗后, 两组 LN、HA 水平均显著降低, 且观察组上述指标均低于对照组 ($P<0.05$); 两组不良反应总发生率为 10.64%、14.89%, 组间比较差异无统计学意义 ($P>0.05$)。结论: 托伐普坦联合氢氯噻嗪治疗慢性心力衰竭的临床效果显著优于单用氢氯噻嗪治疗, 可有效改善患者血清 Hcy、NTpro-BNP 水平, 且不会增加不良反应。

关键词: 托伐普坦; 氢氯噻嗪; 慢性心力衰竭; 同型半胱氨酸; N 末端脑钠肽前体

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Efficacy of Topvastatin Combined with Hydrochlorothiazide on Chronic Heart Failure and Its Effect on the Serum Hcy and NTpro-BNP Levels*

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ABSTRACT Objective: To study the efficacy of topvastatin combined with hydrochlorothiazide in the treatment of chronic heart failure and its effect on the serum Homocysteine (Hcy), n-terminal brain natriuretic peptide precursor (NTproBNP) levels. **Methods:** 94 patients with chronic heart failure who were treated in our hospital from January 2018 to December 2019 were selected and divided into the observation group (n=47) and the control group (n=47) by drawing lots. The control group was treated with hydrochlorothiazide, while the observation group was treated with topvastatin on the basis of control group. The clinical efficacy, changes of serum Hcy, NTproBNP, LVESD, LVEF, 6min walking distance, laminin (LN), hyaluronic acid (HA) levels before and after treatment and incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of the two groups was 93.62% and 74.47%, respectively, which was significantly higher in the observation group than in the control group ($P<0.05$). Before treatment, there was no significant difference in the serum Hcy and NTproBNP levels between the two groups. After treatment, serum levels of Hcy and NTproBNP in the two groups were significantly lower than those before treatment, and the above indexes in the observation group were significantly lower than those in the control group ($P<0.05$). Before treatment, there was no significant difference in the LVESD, LVEF and 6 min walking distance between the two groups. After treatment, the level of LVEF and 6 min walking distance in both groups was significantly higher than that before treatment, and the level of LVESD in the observation group was significantly higher than that in the control group, while the level of LVESD in the two groups was significantly lower than that before treatment, and the level of LVESD in the observation group was significantly lower than that in the control group ($P<0.05$). Before treatment, there was no significant difference in myocardial fibrosis index between the two groups. After treatment, the levels of LN and HA in both groups were significantly reduced, and the above indexes in the observation group were lower than those in the control group ($P<0.05$). The total incidence of adverse reactions between the two groups was 10.64% and 14.89%, and no statistically significant difference was found between the two groups ($P>0.05$). **Conclusion:** The clinical effect of topvastatin combined with hydrochlorothiazide in the treatment of chronic heart fail-

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ure was significantly better than that of hydrochlorothiazide alone, which could effectively improve the serum levels of Hcy and nt-pro-bnp without increasing adverse reactions.

Key words: Topvastatin; Hydrochlorothiazide; Chronic heart failure; Homocysteine; N-terminal brain natriuretic peptide precursor

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前言

慢性心力衰竭是心血管内科常见疾病,是各种心血管事件发展的终末阶段,预后差、病死率高,主要由心肌损害及心室过重负荷所致,临床表现为呼吸困难、液体潴留及心悸等症状^[1,2]。近年来,随着我国人口老龄化的加剧,慢性心力衰竭的发病率逐年升高,相关研究表明我国 35~74 岁的居民中慢性心力衰竭的患病率高达 0.9%,且呈逐年升高^[3]。因此,积极探讨慢性心力衰竭的治疗方案具有重要意义。

氢氯噻嗪属利尿剂可降低血管壁张力,减少心脏后负荷,从而改善患者心功能,但其单独治疗效果一般^[4,6]。托伐普坦是近几年应用于临床的精氨酸加压素受体拮抗药,对肾脏的重吸收具有限制作用,因而纠正患者电解质紊乱^[7,8]。同型半胱氨酸(Hcy)是蛋氨酸代谢的中间产物,可直接损伤血管内皮细胞,提高心血管疾病发病的风险;N 末端脑钠肽前体 (NTpro-BNP)属于心肌细胞所产生的多肽类物质,被广泛运用在心力衰竭患者的诊断中^[9,10]。此外,有研究显示 Hcy、NTpro-BNP 参与了多种心血管疾病的发生^[11]。本研究旨在探讨托伐普坦联合氢氯噻嗪治疗慢性心力衰竭的疗效,及其对患者血清 Hcy、NTpro-BNP 水平的影响,现将结果报道如下。

1 资料与方法

1.1 一般资料

选择 2018 年 1 月-2019 年 12 月在我院接受治疗的 94 例慢性心力衰竭患者。采用抽签法分为 2 组,观察组 47 例:男 26 例,女 21 例,年龄 51-83 岁,平均 (63.56 ± 4.15) 岁,心功能分级:II 级 19 例、III 级 18 例、IV 级 10 例;病程 11 月~2 年,平均 (1.45 ± 0.16) 年;对照组 47 例,男 25 例,女 22 例,年龄 52-82 岁,平均 (63.61 ± 4.21) 岁,心功能分级:II 级 21 例、III 级 15 例、IV 级 11 例;病程 10 月~2 年,平均 (1.41 ± 0.17) 年。两组基线资料比较无明显差异($P>0.05$),具有可比性。

慢性心力衰竭的诊断参照《中国急性心力衰竭急诊临床实践指南》^[12],(1)伴有劳力性呼吸困难,运动耐量降低;(2)心脏杂音、颈静脉扩张;(3)LVEF $<40\%$;(4)影像检测确诊。纳入标准:

(1)符合上述诊断标准;(2)临床资料完整;(3)血流动力学稳定;(4)病情稳定,无生命危险;(5)签署知情同意书。排除标准:(1)重症有生命危险患者;(2)患有意识障碍、精神障碍者;(3)急性心肌梗死患者;(4)合并严重心律失常患者;(5)急性感染者;(6)心源性休克患者;(7)依从性较差者;(8)对本次研究药物过敏者。

1.2 治疗方法

两组均给予利尿、吸氧、电解质纠正等常规治疗。对照组给予氢氯噻嗪(规格:6.25 mg,生产厂家:浙江华海药业股份有限公司,国药准字:H20058709)25 mg/次,1 d 1 次。观察组在对照组的基础上加用托伐普坦(规格:15 mg;生产厂家:浙江大冢制药有限公司;国药准字 H20110115)15 mg/次,1 d 1 次。两组均连续治疗 7 d。

1.3 观察指标

采集空腹静脉血 5 mL,以 $3000 \text{ r} \cdot \text{min}^{-1}$ 的速度进行离心,时间 10 min,提取上层血清后,置于零下 20℃ 的冷冻箱内存储以备检测,采用双抗体夹心酶联免疫吸附法测定同型半胱氨酸(Hcy)、N 末端脑钠肽前体(NTpro-BNP)、层黏连蛋白(LN)、透明质酸(HA)水平;使用超声心动图测量左室收缩末期内径(LVESD)、左心室射血分数(LVEF);记录 6 min 步行距离及不良反应发生情况。

疗效评定标准:显效:与治疗前比较,心功能改善 >2 级;有效:与治疗前比较,心功能改善 1~2 级;无效:临床症状无明显改善甚至加重。

1.4 统计学分析

以 SPSS18.0 软件包处理实验数据,符合正态分布计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示,组间比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组疗效的比较

治疗后,两组总有效率分别为 93.62%,74.47%,观察组显著高于对照组($P<0.05$),见表 1。

表 1 两组临床疗效的比较[例(%)]

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

Groups	n	Excellent	Valid	Invalid	Total effective rate
Observation group	47	29(61.70)	15(31.91)	3(6.38)	44(93.62)
Control group	47	18(38.30)	17(36.17)	12(25.53)	35(74.47)
χ^2 value					6.425
P value					0.011

2.2 两组治疗前后血清 Hcy、NTpro-BNP 水平的比较

治疗前,两组血清 Hcy、NTpro-BNP 水平比较无明显差异;

治疗后,两组血清 Hcy、NTpro-BNP 水平均较治疗前显著降低,且观察组上述指标均明显低于对照组($P<0.05$),见表 2。

表 2 两组治疗前后血清 Hcy、NTpro-BNP 水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the serum Hcy and ntpro-bnp levels between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Hcy(mmol/L)		NTpro-BNP(pg/mL)	
		Before the treatment	After treatment	Before the treatment	After treatment
Observation group	47	19.18 $\pm$ 4.14	12.31 $\pm$ 3.12	5504.35 $\pm$ 761.24	2561.24 $\pm$ 521.36
Control group	47	19.23 $\pm$ 4.11	15.41 $\pm$ 4.31	5512.25 $\pm$ 763.87	4049.63 $\pm$ 304.15
t value		0.059	3.994	0.050	16.905
P value		0.953	0.000	0.960	0.000

2.3 两组治疗前后心功能的比较

治疗前, 两组 LVESD、LVEF、6 min 步行距离水平比较无明显差异; 治疗后, 两组 LVEF、6 min 步行距离水平均较治疗

前显著升高, 且观察组以上指标均明显高于对照组, 两组 LVESD 水平较治疗前显著下降, 且观察组显著低于对照组 ($P<0.05$), 见表 3。

表 3 两组治疗前后心功能水平比较($\bar{x} \pm s$)

Table 3 Comparison of the cardiac function between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	LVESD(mm)		LVEF(%)		6 min walking distance(m)	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Observation group	47	54.73 $\pm$ 5.29	31.51 $\pm$ 3.76	28.52 $\pm$ 2.60	47.91 $\pm$ 4.13	156.59 $\pm$ 14.84	478.53 $\pm$ 23.48
Control group	47	54.75 $\pm$ 5.33	40.83 $\pm$ 4.27	28.47 $\pm$ 2.65	39.88 $\pm$ 3.19	157.05 $\pm$ 14.93	358.37 $\pm$ 17.49
t value		0.018	11.230	0.092	10.549	0.149	28.136
P value		0.985	0.000	0.927	0.000	0.881	0.000

3 讨论

慢性心力衰竭是由多种因素所致的心肌受损, 从而导致心肌功能改变引发的临床综合征, 多发生于老年人, 若得不到及时有效治疗则会引起患者死亡^[13-15]。该病发病率高达 39.8%, 住院率约占心血管疾病总住院率的 19.8%, 调查显示我国心力衰竭发病率低于发达国家, 但我国人口老龄化严峻, 导致其发病率不断升高。因此, 及时有效治疗对改善慢性心力衰竭患者的预后极为重要^[16]。有研究显示慢性心力衰竭是由于肾素-血管紧张素系统过度激活而导致血管壁 Na^+ 浓度增加, 降低了心的输出量, 可引起机体周围器官组织因血液循环不足而发生功能障碍^[17]。因此, 临床常采用扩血管、利尿剂等药物以减轻心脏负荷, 降低心率, 最终达到改善心肌代谢、纠正慢性心力衰竭的目的。

氢氯噻嗪属于中效利尿剂, 可于口服 2 h 内迅速起效, 4 h 时可达到最强利尿作用, 可通过减少血管壁 Na^+ 浓度而加快水、 Na^+ 代谢, 抑制远端肾曲小管 Na^+-Cl^- 交换, 有效降低外周血管阻力, 改善外周水肿, 减轻心脏负荷, 改善心功能^[18-20]。但氢氯噻嗪单独治疗效果不佳, 且利尿药物可造成电解质紊乱、肾功能不全及利尿剂抵抗等不良反应, 故较多学者提出在此基础上联合治疗^[21]。有研究显示精氨酸加压素水平表达与心力衰竭严重程度有关, 在心力衰竭的发病中具有重要意义^[22]。当心力衰竭发生时, 心房牵张受体敏感度降低, 使精氨酸加压素释放, 引起电解质紊乱及增加液体滞留量, 进一步导致心力衰竭恶化。因此, 阻止精氨酸血管加压素的作用可作为治疗心力衰竭的新途径^[23-25]。托伐普坦是近几年应用于临床的精氨酸加压素受体拮抗药, 能够选择性和竞争性地抑制血管加压素与 V2 受体结合, 有助于机体血钠水平的升高, 使尿液中的水分含量减少, 抑

制肾集合管对水重吸收而不增加电解质排出, 从而纠正电解质紊乱^[26]。本研究结果显示联合托伐普坦治疗的患者总有效率为 93.62%, 明显高于对照组, 提示联合托伐普坦治疗慢性心力衰竭可提高患者的治疗效果, 分析其原因可能是因为氢氯噻嗪可改善心内膜下心肌血流灌注, 降低室壁肌张力; 托伐普坦可在短时间内增加患者 24h 尿量, 减轻体重, 两种药物联合治疗, 改善患者临床症状, 从而提高治疗效果。研究还显示, 两组不良反应发生率无明显差异, 说明联合治疗不会提高不良反应发生率。国外研究也显示托伐普坦可减少肾脏对水的重吸收, 减轻心脏负荷, 在排水的同时不会增加钠离子排泄量, 用药安全可靠^[27]。

Hcy 是蛋氨酸代谢产生的含巯基的氨基酸, 与多种心脑血管疾病的发生存在关系, Hcy 可促进氧自由基产生, 损伤血管内皮细胞, 导致血管舒张障碍。有研究显示 Hcy 可通过激活基质金属蛋白酶, 诱导炎症因子及促凝物质, 造成心肌间质的纤维化, 导致心肌重构; 还能引起体内凝血障碍, 激活血管脂质形成和钙化, 加重心肌缺血缺氧, 最终引起心脏功能障碍发生慢性心力衰竭。国外研究显示 Hcy 在慢性心力衰竭中表达异常, 其水平可随着患者心功能分级增加而升高。NTpro-BNP 属于心室肌细胞产生的多肽类物质, 当发生心力衰竭时, 患者因心室容积扩张及心肌缺血缺氧可促进其分泌, 使心室肌细胞生成大量前脑钠肽原进入血液循环, 导致心室充盈, 增加体循环及肺循环阻力, 提高心室张力和负荷。NTpro-BNP 主要由心脏分泌, 心室容量及压力增加, 会刺激血浆 NTpro-BNP 释放, 当发生心力衰竭时其水平升高。本研究结果显示观察组治疗后血清 Hcy、NTpro-BNP、LVESD 水平均显著低于对照组, LVEF、6min 步行距离水平均显著高于对照组, 提示联合托伐普坦效果好, 且可有效改善心肌供血、增强心肌收缩力, 改善左心室收缩功能。国外研究也显示托伐普坦用于慢性心力衰竭效果明显,

可在短时间内减轻体重,减少液体潴留,改善患者的心功能。分析其原因可能是因为氢氯噻嗪可改善外周水肿及心内膜下心肌血流灌注,降低室壁肌张力,减少患者心脏负荷,从而改善心功能;而托伐普坦考虑可能与尿量增加,托伐普坦使患者心脏前负荷降低,从而导致心室合成和释放的 Hcy 相对减少,两种药物联合治疗,从而改善患者的心功能。本研究中,观察组治疗后 LN、HA 水平均显著低于对照组,提示联合托伐普坦治疗能减轻慢性心力衰竭患者心肌纤维化。

综上所述,托伐普坦联合氢氯噻嗪治疗慢性心力衰竭的临床效果显著优于单用氢氯噻嗪治疗,可有效改善患者血清 Hcy、NTpro-BNP 水平,且不会增加不良反应。

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