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不同剂量辛伐他汀联合曲美他嗪对慢性心力衰竭患者血脂及血清 IL-6、TNF- α 、BNP 水平的影响*

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摘要 目的:探讨不同剂量辛伐他汀联合曲美他嗪对慢性心力衰竭(CHF)患者血脂及血清白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)、脑钠肽(BNP)水平的影响,为临床用药提供参考。**方法:**研究对象为2015年1月至2016年6月我院收治的146例CHF患者,将其根据随机数字表法分为两组,其中对照组(n=73)采用常规剂量辛伐他汀(20 mg/d)联合曲美他嗪治疗,观察组(n=73)采用强化剂量辛伐他汀(40 mg/d)联合曲美他嗪治疗,两组均治疗6个月。观察两组疗效,同时测定并比较治疗前后两组患者心功能指标、血脂指标以及炎症因子的变化情况。**结果:**观察组总有效率为94.52%,明显高于对照组的82.19%($P<0.05$)。治疗后,观察组的LVEF明显高于对照组,而LVEDD、LVESD明显低于对照组($P<0.05$)。治疗后,观察组的TC、TG、LDL-C、IL-6、TNF- α 、BNP水平明显低于对照组,而HDL-C水平明显高于对照组($P<0.05$)。两组均无严重不良反应发生。**结论:**与常规剂量比较,强化剂量辛伐他汀(40 mg/d)联合曲美他嗪治疗CHF具有更好的疗效,对心功能、血脂及炎症因子有更好的改善作用。

关键词:辛伐他汀;曲美他嗪;慢性心力衰竭;血脂;炎症因子

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Chronic Heart Failure: Effects of Different Doses of Simvastatin plus Trimetazidine on Blood Lipid and Serum IL-6, TNF- α and BNP Levels*

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ABSTRACT Objective: To investigate the effects of different doses of simvastatin combined with trimetazidine on blood lipid and serum Interleukin-6 (IL-6), tumor necrosis factor - α (TNF- α) and brain natriuretic peptide (BNP) levels in patients with chronic heart failure (CHF), so as to provide references for clinical medication. **Methods:** A total of 146 CHF patients, who were treated in Guilin People's Hospital from January 2015 to June 2016, were selected and randomly divided into two groups. The control group (n=73) was treated with conventional dose (20 mg/d) simvastatin combined with trimetazidine, while the observation group (n=73) was treated with intensive dose (40 mg/d) simvastatin combined with trimetazidine. The two groups were treated for 6 months. The effects of the two groups were observed and the changes of cardiac function index, blood lipid index and inflammatory factors were measured and compared in the two groups before and after treatment. **Results:** The total effective rate (94.52%) of the observation group was significantly higher than that (82.19%) of the control group ($P<0.05$). After treatment, the LVEF of the observation group was significantly higher than that of the control group, while the LVEDD and LVESD were significantly lower than those of the control group ($P<0.05$). After treatment, the levels of TC, TG, LDL-C, IL-6, TNF- α and BNP in the observation group were significantly lower than those in the control group, while the HDL-C level was significantly higher than that of the control group ($P<0.05$). There was no serious adverse reaction in the two groups. **Conclusion:** Compared with routine dose, intensive dose simvastatin (40 mg/d) combined with trimetazidine in the treatment of CHF has better effect, which has better effect on cardiac function, blood lipid and inflammatory factors.

Key words: Simvastatin; Trimetazidine; Chronic heart failure; Blood lipids; Inflammatory factors

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前言

慢性心力衰竭(chronic heart failure, CHF)是多种心脏疾患终末期的常见表现,是以左室心肌舒缩障碍、运动减弱为特征,心排血量不足以供给机体代谢,导致循环受限、机体重要组织、

器官衰竭的一种常见临床综合征^[1,2]。近年来,CHF的发病率呈现出逐年增高的趋势,尽管临床上对其治疗有了更为深入的认识,然而CHF的5年死亡率仍处于较高的水平^[3]。有研究表明^[4],患者的血脂水平,可以在一定程度上反映CHF的严重程度。同时,目前普遍认为,心室重构是CHF的重要发病机制之一,

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而细胞炎性因子是导致心肌细胞的肥大和纤维化的重要原因,其可对心肌细胞的坏死、凋亡起到促进作用,进一步引发心室重构^[5,6]。辛伐他汀是临床治疗 CHF 的常用药物,在改善患者血流变学及炎性反应方面有着较好的作用^[7,8],但其使用的剂量问题,仍然存在争议。本研究采用不同剂量辛伐他汀联合曲美他嗪对 CHF 进行治疗,以期明确辛伐他汀的剂量与其对 CHF 的疗效的关系,为临床剂量的选择提供参考依据。现报道如下。

1 资料与方法

1.1 一般资料

选取我院在 2015 年 1 月至 2016 年 6 月间收治的 146 例 CHF 患者,按随机数字表法均分为对照组与观察组。纳入标准^[9,10]:① 均符合《中国心力衰竭诊断和治疗指南》中的相关诊断标准;② 经超声心动图检测,患者左心室射血分数(Left ventricular ejection fraction, LVEF)小于等于 40%;③ 患者心功能 NYHA 分级 II~IV 级;④ 患者入院前 1 个月均未服用具有调制作用的药物以及他汀类药物;⑤ 患者及家属均知情同意。排除标准:① 合并全身免疫性疾病者;② 合并恶性肿瘤者;③ 严重肝、肾功能不全者;④ 妊娠及哺乳期妇女。对照组男 42 例,女 31 例,年龄 43~76 岁,平均(62.37±6.85)岁,病程 8 个月~11 年,平均(4.89±2.02)年,NYHA 分级:II 级 16 例,III 级 23 例,IV 级 34 例。观察组男 40 例,女 33 例,年龄 41~77 岁,平均(63.43±7.27)岁,病程 8 个月~11 年,平均(5.13±1.97)年,NYHA 分级:II 级 15 例,III 级 25 例,IV 级 33 例。两组患者一般资料比较差异无统计学意义($P>0.05$)。本研究已经医院伦理委员会批准通过。

1.2 治疗方法

两组患者均给予吸氧、利尿剂、洋地黄制剂、血管扩张剂等,进行常规抗心衰治疗。对照组在此基础上加用常规剂量辛伐他汀联合曲美他嗪治疗:辛伐他汀(宜昌人福药业,国药准字 H20103420,规格:10 mg)口服,20 mg/次,1 次/d;曲美他嗪(瑞阳制药有限公司,国药准字 H20066534,规格:20 mg)20 mg/次口服,3 次/d,持续治疗 6 个月。在常规抗心衰治疗基础上,观

察组采用强化剂量辛伐他汀联合曲美他嗪治疗:辛伐他汀口服,40 mg/次,1 次/d;曲美他嗪,20 mg/次口服,3 次/d,持续治疗 6 个月。

1.3 观察指标

1.3.1 心功能检测 所有患者均于治疗前及治疗 6 个月后(治疗后)采用心脏彩色多普勒超声仪(美国 GE 公司,ViViD E9 型)检测心功能指标,探头频率设置为 3.5~5.0MHz,采用辛普森法测定 LVEF、左心室舒张末期内径(LVEDD)、左心室收缩末期内径(LVESD)。

1.3.2 血脂检测 所有患者均于治疗前及治疗 6 个月后(治疗后)的清晨,取空腹肘静脉血 5 mL,采用罗氏 C8000 全自动生化分析仪测定患者总胆固醇(TC)、三酰甘油(TG)、高密度脂蛋白胆固醇(HDL-C)和低密度脂蛋白胆固醇(LDL-C)。

1.3.3 炎性因子检测 所有患者均于治疗前及治疗 6 个月后(治疗后)的清晨,取空腹肘静脉血 5 mL,分离血清。血清白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)外送广州金域医学检验集团检测,血清脑钠肽(BNP)水平采用电化学发光法测定。试剂盒购自德国罗氏诊断有限公司,操作均严格按说明书进行。

1.4 疗效评定^[11]

疗效均根据患者治疗前后的临床特征及 NYHA 分级变化进行评定:显效:患者临床症状明显改善或消失,NYHA 分级改善 ≥ 2 级;有效:患者临床症状得到一定改善,NYHA 分级改善达到 1 级;无效:患者临床症状无改善甚至恶化。总有效率=显效率+有效率。

1.5 统计学方法

本研究数据均采用 SPSS19.0 软件处理。计数资料以[n(%)]表示,采用 χ^2 检验,计量资料以($\bar{x}\pm s$)表示,采用双侧 t 检验。检验标准设为 $\alpha=0.05$ 。

2 结果

2.1 两组治疗效果比较

观察组总有效率为 94.52%(69/73),明显高于对照组的 82.19%(60/73)($P<0.05$)。见表 1。

表 1 两组治疗效果比较[n(%)]

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

Groups	Cases	Effective	Valid	Invalid	Total effective rate
Control group	73	36(49.32)	24(32.88)	13(17.81)	60(82.19)
Observation group	73	42(57.53)	27(36.97)	4(5.48)	69(94.52)
χ^2	-				5.393
P	-				0.020

2.2 两组患者心功能指标比较

两组患者心功能指标比较情况见表 2。与治疗前相比,两组患者治疗后的 LVEF 均明显升高,而 LVEDD、LVESD 明显降低($P<0.05$)。与对照组相比,观察组治疗后的 LVEF 明显较高,而 LVEDD、LVESD 明显较低($P<0.05$)。

2.3 两组患者血脂水平比较

两组患者血脂水平指标比较情况见表 3。与治疗前比较,两组患者治疗后的 TC、TG、LDL-C 水平均明显降低,而

HDL-C 水平明显升高($P<0.05$)。与对照组比较,观察组治疗后的 TC、TG、LDL-C 水平明显较低,而 HDL-C 水平明显较高($P<0.05$)。

2.4 两组患者 IL-6、TNF- α 、BNP 水平比较

两组患者炎性因子水平比较情况见表 4。与治疗前比较,两组患者治疗后的 IL-6、TNF- α 、BNP 水平均明显降低($P<0.05$)。与对照组比较,观察组治疗后的 IL-6、TNF- α 、BNP 水平明显较低($P<0.05$)。

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

Groups	LVEF(%)		LVEDD(mm)		LVESD(mm)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=73)	40.95± 3.46	49.69± 2.14*	63.13± 4.52	54.74± 3.63*	47.79± 3.87	40.96± 2.93*
Observation group (n=73)	41.21± 3.64	55.93± 2.46*	62.76± 5.13	48.31± 3.27*	48.01± 3.81	35.84± 3.34*
t	0.442	16.351	0.462	11.245	0.346	21.384
P	0.659	0.000	0.645	0.000	0.730	0.000

Note: Compared with before treatment,* $P<0.05$.表 3 两组患者血脂水平比较 (mmol/L, $\bar{x} \pm s$)Table 3 Comparison of blood lipid levels between two groups (mmol/L, $\bar{x} \pm s$)

Groups	TC		TG		HDL-C		LDL-C	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=73)	5.86± 0.63	4.62± 0.54*	2.43± 0.58	2.01± 0.36*	0.86± 0.21	0.94± 0.15*	3.98± 0.69	3.62± 0.43*
Observation group (n=73)	5.91± 0.68	3.69± 0.31*	2.40± 0.55	1.74± 0.21*	0.84± 0.23	1.11± 0.12*	3.92± 0.71	3.11± 0.37*
t	0.461	12.761	0.321	5.535	0.549	7.610	0.518	7.681
P	0.646	0.000	0.749	0.000	0.584	0.000	0.605	0.000

Note: Compared with before treatment,* $P<0.05$.表 4 两组患者 IL-6、TNF- α 、BNP 水平比较 (ng/L, $\bar{x} \pm s$)Table 4 Comparison of IL-6, TNF- α and BNP levels between two groups (ng/L, $\bar{x} \pm s$)

Groups	IL-6		TNF- α		BNP	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=73)	62.63± 3.89	51.35± 3.36*	193.82± 18.35	152.28± 12.44*	1654.34± 146.21	894.85± 124.39*
Observation group (n=73)	62.16± 3.74	44.23± 2.89*	197.41± 16.97	118.62± 11.59*	1673.58± 143.78	467.18± 121.01*
t	0.744	13.726	1.227	16.915	0.802	21.056
P	0.458	0.000	0.222	0.000	0.424	0.000

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

2.5 不良反应情况

研究过程中所有患者均未出现严重不良反应。两组各出现 1 例腹胀,均不影响后续治疗。

3 讨论

CHF 的传统治疗模式主要包括利尿、强心和扩张血管等^[12]。而随着对 CHF 发病机制的进一步深入研究,临床治疗 CHF 也逐渐由单纯的改善患者血流动力学,逐渐转化为神经内分泌综合调控的模式,因此 β 受体阻滞剂、醛固酮拮抗剂、血管紧张素受体拮抗剂等药物也被应用于 CHF 的治疗中^[13,14]。但因患者个体的不同,部分患者对上述药品耐受力不足,因而在临床治疗时,此类患者心力衰竭反复发作,病情得不到较好的控制。他汀类药物具有调脂、调节炎症反应的作用,同时能够对细胞粘附、内皮功能、平滑肌增殖和血栓形成过程等产生影响,过往在心脏疾病的治疗中应用较为广泛^[15-17]。辛伐他汀是一种他汀类药物,过往临床实践中将其应用于 CHF 可有效平衡患者机体胆固醇,对机体血脂有很好的调节作用,从而能有效预防不良心血管事件的发生^[18]。而曲美他嗪可通过选择性地抑制线粒体

酶活性,以及对游离脂肪酸合成磷脂这一过程的促进,促进葡萄糖氧化、使缺氧心肌细胞的氧利用率得到提高,并起到稳定心肌细胞膜和促进心肌细胞功能恢复的作用^[19-21]。IL-6 可诱导机体产生 NO,从而使心肌的收缩能力减弱;TNF- α 参与了对心肌细胞肌力的负性作用,并加速了心室重构;BNP 水平则与心功能密切相关,三者均是近年来研究较多的心血管事件炎性标志物^[22-24]。研究表明,CHF 患者血清 IL-6、TNF- α 、BNP 水平均存在异常升高^[25]。辛伐他汀可通过抑制炎症反应的重要转录因子 NF- κ B 的活性、激活过氧化物酶活化受体,从而使 CHF 患者体内的炎症反应减弱。同时,辛伐他汀还可通过平衡 CHF 患者体内的氧自由基、抑制神经内分泌激素等途径,起到延缓心衰的进展的作用。

过往临床实践证明^[26],CHF 患者采用辛伐他汀联合曲美他嗪治疗,其效果值得肯定,但辛伐他汀的使用剂量问题仍存在一定争议。许多研究均表明^[27,28],与常规剂量辛伐他汀比较,低剂量辛伐他汀对患者心功能和炎症反应的改善效果较差。张海伶等人的研究中,高剂量辛伐他汀(40 mg/d)联合曲美他嗪治疗 CHF 取得了更好的疗效,但廖雪松的研究认为,提高辛伐他

汀的剂量,并不能使治疗效果得到相应的提升。本研究采用高剂量和常规剂量辛伐他汀联合曲美他嗪对 CHF 患者进行治疗,结果发现,采用高剂量辛伐他汀的观察组总有效率明显高于对照组,同时观察组患者的心功能指标、血脂水平、炎症因子水平均优于对照组,且两组均未出现严重不良反应,提示 40 mg/d 剂量的辛伐他汀联合曲美他嗪治疗 CHF 相比于常规剂量的辛伐他汀疗效更好,同时也具有一定的安全性。但本研究设置的剂量梯度较少,临床治疗 CHF 采用的辛伐他汀的最佳剂量仍需更多的临床数据资料进行研究确定。

综上所述,与常规剂量比较,强化剂量辛伐他汀(40 mg/d)联合曲美他嗪治疗 CHF 具有更好的疗效,对心功能、血脂及炎症因子有更好的改善作用,且安全性良好,值得在临床中推广应用。

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