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不同剂量阿托伐他汀对老年急性冠脉综合征患者经 PCI 术后血清炎症因子水平和内皮功能的影响 *

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摘要 目的：探讨不同剂量阿托伐他汀对老年急性冠脉综合征患者经 PCI(经皮冠状动脉介入治疗，percutaneous coronary intervention)术后血脂、血清炎症因子水平及血管内皮功能的影响。**方法**：选取 2015 年 8 月至 2017 年 4 月我院收治的老年急性冠脉综合征患者 80 例，依据随机数据表法分为观察组和对照组，每组 40 例。对照组给予小剂量阿托伐他汀(20 mg/d)治疗，观察组给予大剂量阿托伐他汀(40 mg/d)治疗。比较两组治疗前后总胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)、低密度脂蛋白胆固醇(low-density lipoprotein, LDL-C)、高密度脂蛋白胆固醇(high-density lipoprotein, HDL-C)、超敏 C 反应蛋白(hypersensitive C-reactive protein, hs-CRP)、白介素 -6(interleukin-6, IL-6)、肿瘤坏死因子(tumor necrosis factor-α，TNF-α)、一氧化氮(nitric oxide, NO)及内皮素 -1(endothelin-1, ET-1)水平的变化。**结果**：治疗前，两组血清 TC、TG、LDL-C、HDL-C、hs-CRP、IL-6、TNF-α、NO 及 ET-1 水平比较差异均无统计学意义(P＞0.05)；治疗后，两组血清 TC、TG、LDL-C、hs-CRP、IL-6、TNF-α 及 ET-1 水平与本组治疗前相比均显著性降低，且观察组治疗后血清 TC、TG、LDL-C、hs-CRP、IL-6、TNF-α 及 ET-1 的水平均显著低于对照组(P<0.05)；两组血清 HDL-C、NO 水平与治疗前相比均显著性升高(P<0.05)，且观察组治疗后的血清 HDL-C、NO 水平显著高于对照组(P<0.05)。**结论**：阿托伐他汀用于经 PCI 术治疗的老年 ACS 患者可显著减轻再灌注后的炎症反应，降低血脂水平并改善内皮功能，且大剂量阿托伐他汀的治疗效果明显优于小剂量治疗。

关键词：阿托伐他汀；急性冠脉综合征；血脂；炎症因子；血管内皮功能

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Effects of Different Doses of Atorvastatin on the Blood Lipid, Serum Inflammatory Factors Levels and Vascular Endothelial Function of Elderly Patients with Acute Coronary Syndrome after PCI*

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ABSTRACT Objective: To investigate the effects of different dosages of atorvastatin on the blood lipid, inflammatory factors and vascular endothelial function of patients with acute coronary syndrome (ACS). **Methods:** According to random data table method, a total of 80 patients with ACS from August 2015 to April 2017 were divided into the observation group and the control group, with 40 cases in each group. The control group was treated with small dose atorvastatin (20 mg/d); the observation group was given large dose atorvastatin (40 mg/d). The levels of serum TC, TG, LDL-C, HDL-C, hs-CRP, IL-6, TNF-α, NO and ET-1 in two groups before and after treatment were compared. **Results:** The levels of serum TC, TG, LDL-C, HDL-C, hs-CRP, IL-6, TNF-α, NO and ET-1in both groups before treatment showed no statistically significant difference (P>0.05). After treatment, the levels of serum TC, TG, LDL-C, hs-CRP, IL-6, TNF-α and ET-1 in both groups were significantly lower than those in the same group before treatment (P<0.05), and which were significantly lower in the observation group than those of the control group; the levels of serum HDL-C, NO in both groups after treatment were significantly higher than those in the same group before treatment(P<0.05), which were significantly higher in the observation group than those of the control group (P<0.05). **Conclusion:** For elderly patients with ACS undergoing PCI surgery, atorvastatin can better reduce the inflammatory response factors, lower the level of blood lipids and improve endothelial function, and the effect of high-dose treatment was significantly better than low-dose treatment.

Key words: Atorvastatin; Acute coronary syndrome; Blood lipid; Inflammatory factors; Vascular endothelial function

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前言

ACS(急性冠状动脉综合征,acute coronary syndromes)主要是由于冠状动脉粥样斑块破裂出血引起急性血栓的形成,进一步加重冠脉狭窄,导致心肌供血不足而引起的一种较为严重的心血管疾病,包括急性 ST 段抬高性心肌梗死、急性非 ST 段抬高性心肌梗死和不稳定型心绞痛(UA)[1-3]。伴随全球老龄化加速及生活方式的改变,老年 ACS 患者的日益增多,并且其临床表现和预后情况复杂,治疗较为困难[4]。近年来,PCI 在老年 ACS 的治疗中取得重大进展,但常伴有灌注损伤和炎症反应等问题[5,6]。他汀类药物具有降脂、抗炎及改善血管内皮功能等多重作用[7,8]。本研究拟从血脂、炎症反应及血管内皮功能三方面探讨不同剂量阿托伐他汀对老年 ACS 患者经 PCI 术后的治疗效果,结果报道如下。

1 对象与方法

1.1 研究对象

选取 2015 年 8 月至 2017 年 4 月在我院接受 PCI 手术治疗的老年急性冠脉综合征患者 80 例，研究对象均符合美国心脏病协会和欧洲心脏病学会制定的 ACS 标准，均伴有阵发性或持续性心前区疼痛,并经心电图、心肌酶检查确诊为不稳定型心绞痛或急性心肌梗死。排除标准:① 治疗前 1 个月内曾服用他汀类及降脂药物;② 患有急慢性炎症、严重肝肾肺功能不全者;③ 对他汀类药物过敏者;④ 患有内分泌疾病者;⑤ 长期接受糖皮质激素、抗生素及免疫抑制剂治疗;⑥ 未能按疗程完成治疗,中途脱落病例,且入院时临床资料不全者。依据随机数据表法将患者分为观察组和对照组。对照组 40 例(给予小剂量阿托伐他汀治疗 20 g/d),男性 26 例,女性 14 例;年龄 61～69 岁。观察组(给予大剂量阿托伐他汀治疗 40g/d)40 例,男性 28 例,女性 12 例;年龄 61～67 岁。两组性别、年龄量等比较差异无统计学意义(P>0.05),组间具有可比性。

1.2 治疗方法

两组患者均在常规治疗的基础上分别于 PCI 术后当日同时加用阿托伐他汀(商品名:立普妥,辉瑞制药有限公司提供),对照组 20 mg/d,观察组 40 mg/d,均为晚饭后顿服,连续用药 4 周。

1.3 观察指标

两组患者分别在治疗前和治疗后进行血脂、血清炎症因子及血管内皮功能的检测。分别在清晨时抽取患者肘静脉血 5 mL,置普通试管中静置几分钟,随后 3000 r/min,离心 10 min,收集上清于 EP 管中,放置在 -20℃冰箱中待测。① 血脂水平:包括 TC、TG、LDL-C、HDL-C 水平测定在德国 Bayer-1650 全自动生化分析仪上进行。② 血清炎症因子的检测:TNF-α 的检测采用放射免疫法，试剂盒购于上海恒远生物公司;IL-6 的检测采用酶联免疫法，试剂盒购自上海超研生物科技有限公司;hs-CRP 的检测采用乳胶增强免疫透射法，试剂盒购自上海复星长征医学公司。操作过程严格按说明书进行。③ 血管内皮功能检测,采用硝酸盐还原酶法测定 NO,试剂盒为硝酸还原酶试剂盒(购自上海仁捷生物科技有限公司),采用放射免疫法测定内皮素 -1(ET-1),选用内皮素试剂盒(上海恪敏生物科技有限公司提供)。

1.4 统计学分析

所得数据应用 SPSS17.0 软件进行统计学分析。符合正态分布的计量资料以($\bar{x}\pm s$)表示,组内治疗前后及组间治疗后各指标比较采用 t 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后血脂水平的比较

治疗前，两组血清 TC、TG、LDL-C、HDL-C 水平比较差异无统计学意义(P＞0.05)。治疗后,两组血清 TC、TG、LDL-C 水平与本组治疗前相比均显著性降低(P＜0.05);观察组治疗后的血清 TC、TG、LDL-C 水平分别为 (3.11± 0.15) mmol/L、(2.05± 0.11)mmol/L、(1.59± 0.16) mmol/L,均显著低于对照组治疗后,差异有统计学意义(P<0.05)。治疗后,观察组血清 HDL-C 水平为(2.36± 0.33)mmol/L,较组内治疗前显著升高,且显著高于对照组治疗后[(1.67± 0.29)mmol/L](P<0.05)。见表 1。

表 1 两组治疗前后血脂水平的比较($\bar{x}\pm s$)

Table 1 Comparison of the blood lipid levels between the two groups before and after treatment($\bar{x}\pm s$)

Group	Cases	Time	TC(mmol/L)	TG(mmol/L)	LDL-C(mmol/L)	HDL-C(mmol/L)
Control group	40	Before treatment	6.38± 0.23	3.29± 0.67	4.52± 0.56	0.95± 0.32
		After treatment	4.92± 0.16*	2.69± 0.21*	2.11± 0.27*	1.67± 0.29*
Observation group	40	Before treatment	6.41± 0.28	3.32± 0.59	4.48± 0.51	0.93± 0.29
		After treatment	3.11± 0.15*#	2.05± 0.11*#	1.59± 0.16*#	2.36± 0.33*#

Note: compared with pre-treatment in the same group, *P<0.05; compared with post-treatment levels in the control group, #P<0.05.

2.2 两组治疗前后血清炎症因子水平的比较

治疗前,两组血清 hs-CRP、IL-6、TNF-α 水平比较差异无统计学意义(P＞0.05)。治疗后,两组血清 hs-CRP、IL-6、TNF-α 水平与本组治疗前相比均显著降低(P＜0.05);观察组治疗后的血清 hs-CRP、IL-6、TNF-α 水平分别为 (13.11 ± 3.56) mg/L、(20.35± 4.11) μg/L、(40.19± 2.53) μg/L，均显著低于对照组治疗后 [(19.2 ± 4.16)mg/L、(25.85 ± 4.36)μg/L、(51.32 ± 3.27) μg/L],差异有统计学意义(P<0.05)。见表 2。

2.3 两组治疗前后血管内皮功能指标的比较

治疗前，两组血清 NO、ET-1 水平比较差异无统计学意义(P>0.05)。治疗后,观察组血清 NO、ET-1 水平为(81.32± 6.71) μmol/L、(41.39± 4.89)ng/L，与组内治疗前相比,NO 水平显著升高,且显著高于对照组治疗后(63.14± 5.13)μmol/L(P<0.05),ET-1 水平显著降低，且显著低于治疗后对照组 (65.51± 6.18) ng/L,差异有统计学意义(P<0.05),见表 3。

表 2 两组治疗前后血清炎症因子水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the Levels of serum inflammatory cytokines between the two groups before and after treatment($\bar{x}\pm s$)

Group	Cases	Time	hs-CRP(mg/L)	IL-6(ng/L)	TNF-α(μg/L)
Control group	40	Before treatment	25.98± 5.23	48.66± 6.71	72.85± 4.57
		After treatment	19.2± 4.16*	25.85± 4.36*	51.32± 3.27*
Observation group	40	Before treatment	26.11± 5.28	48.21± 6.67	73.79± 4.62
		After treatment	13.11± 3.56*#	20.35± 4.11*#	40.19± 2.53*#

Note: compared with pre-treatment in the same group, *P<0.05; compared with post-treatment levels in the control group, #P<0.05.

表 3 两组治疗前后血管内皮功能指标的比较($\bar{x}\pm s$)

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

Group	Cases	Time	NO(μmol/L)	ET-1(ng/L)
Control group	40	Before treatment	42.32± 4.58	95.76± 8.32
		After treatment	63.14± 5.13*	65.51± 6.18*
Observation group	40	Before treatment	41.98± 4.35	96.13± 8.78
		After treatment	81.32± 6.71*#	41.39± 4.89*#

Note: compared with pre-treatment in the same group, *P<0.05; compared with post-treatment levels in the control group, #P<0.05.

3 讨论

ACS 以往在发达国家中发病率较高。近年来,伴随我国经济的快速发展,国民生活水平逐步提高,居民的饮食结构也发生了巨大改变，高热量及高脂肪食物的过多摄入使我国 ACS 患者日益增多,尤以老年患者居多[9,10]。临床研究显示老年 ACS 患者通常合并有糖尿病、高血压病、心、肾功能不全以及血脂异常等多重危险因素,因此治愈过程较为复杂且预后效果不理想[11-13]。研究表明 ACS 的发生是由于冠状动脉内斑块的不稳定性破裂及继发出血和血栓形成,引起冠状动脉的阻塞所致[14]。近年来,PCI 术作为一种微创型手术在治疗老年 ACS 中取得一系列进展,该治疗方法通过疏通冠状动脉狭窄或闭塞重建冠状动脉血流,挽救心肌缺血从而达到治疗疾病的作用[15]。虽然 PCI 术在对老年 ACS 中具有作用迅速且成功率高等特点，但 ACS 患者经 PCI 时,由于支架的植入会对血管壁造成损失,导致炎症反应加重,因此患者术后心血管事件发生率仍较高[16]。

他汀类药物是一种 HMG-CoA 还原酶 (3- 羟基 -3- 甲基戊二酸单酰辅酶 A 还原酶,3-hydroxy-3-methyl glutaryl coenzyme A reductase)选择性抑制剂,通过降低 TC 及 LDL-C 水平起到调脂作用[17,18]。已有研究表明他汀类药物除具有调脂作用以外,还具有多重作用,包括抑制炎症反应,稳定粥样斑块,改善血管内皮功能等[19]。因此,他汀类药物也被广泛的应用到 ACS 患者 PCI 术后防止心血事件再发生的治疗中。本研究结果显示:两组治疗后 TC、TG、LDL-C 水平与本组治疗前相比均显著性降低,观察组治疗后以上指标均显著低于对照组,而血清 HDL-C 水平显著高于对照组,表明剂量阿托伐他汀(40 mg/d)的调脂疗效明显优于小剂量阿托伐他汀(20 mg/d)。分析原因可能是由于阿托伐他汀在体内竞争性地抑制胆固醇合成过程中的限速酶羟甲戊二酰辅酶 A 还原酶,使胆固醇的合成减少,低密度脂蛋白受体合成增加,TC 和 LDL-C、TG 降低,HDL-C 增高。大剂量他汀较小剂量他汀能更进一步降低 ACS 患者血脂水平并减少主要心血管事件的发生[20,21]。

目前,hs-CRP、IL-6、TNF-α 等细胞因子常被作为 ACS 的炎症标记物,上述因子作为识别易损斑块、预测斑块稳定性的可靠因子具有较高的临床价值[22]。hs-CRP 是由肝细胞合成的一种急相期蛋白,能促进血栓形成,已被证实是由慢性炎症引发不稳定型心绞痛的独立危险因素，检测其浓度对 ACS 的干预及预后起重要作用[23]。IL-6 是一种多功能炎性因子,有促进凝血作用,可刺激肝细胞产生急相期蛋白,参与炎症反应[24]。TNF-α 是主要由单核 - 巨噬细胞分泌的炎性因子，可引起血管内皮细胞损伤,使其通透性增加,血浆脂质沉积在血管壁上形成动脉粥样硬化斑块[25]。本研究结果显示服用阿托伐他汀后,患者血清 hs-CRP、IL-6、TNF-α 水平均较治疗前显著降低,且大剂量阿托伐他汀治疗后血清 hs-CRP、IL-6、TNF-α 水平降低更明显,与陈洪涛[26]证实的大剂量阿托伐他汀能强有力的降低 ACS 患者的炎症反应报道一致。具体原因可能是阿托伐他汀通过抑制细胞内有关信号转导，抑制炎症相关基因的表达，降低 hs-CRP、IL-6、TNF-α 水平,减轻了患者冠状动脉内硬化斑块的炎症反应,有利于斑块的稳定。

血管内皮细胞是介于血流和血管壁组织之间的一层单核细胞,通过分泌 NO、ET-1 等活性物质,起到抗血栓、调节血管紧张的作用。血管内皮细胞在维持血管功能方面起着重要作用[27,28]。正常情况下,ET-1 及 NO 水平处于动态平衡状态以维持血管舒缩功能。血管内皮细胞损伤后,该平衡状态被打破,NO 分泌量减少,导致血管舒张发生障碍,引起血小板聚集加速;ET-1 分泌量增加,血管发生痉挛[29]。近年来,研究表明内皮细胞结构和功能的障碍在 ACS 发生中起着重要作用[30]。本研究结果表明两组患者治疗后血清 NO 水平均明显升高，血清 ET-1 均显著降低，而大剂量阿托伐他汀治疗后的改善程度明显更优,说明大剂量阿托伐他汀改善 ACS 患者血管内皮功能的效果更好。可能原因是阿托伐他汀药物可以促进一氧化氮合酶(NOS)基因的表达,进而增加内皮细胞内 NO 数量,起到舒张血管内皮,改善内皮功能,从而保证组织和器官有充足的血液供应。

综上所述，阿托伐他汀可有效降低 ACS 患者经 PCI 术后

血脂、血清炎症因子水平，促进血管内皮功能的修复，有利于冠状动脉内硬化斑块的稳定性，并且经大剂量阿托伐他汀治疗后效果更好。提示我们在今后的治疗过程中，在无不良反应的情况下，可适当提高阿托伐他汀的用量，以提高治疗效果，进一步降低 ACS 患者经 PCI 术后心血管事件再发生的风险。

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