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阿托伐他汀联合替格瑞洛对冠心病不稳定型心绞痛患者炎性因子、血脂及不良心脏事件的影响*

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摘要 目的:探讨阿托伐他汀联合替格瑞洛对冠心病不稳定型心绞痛(UAP)患者炎性因子、血脂及不良心脏事件的影响。**方法:**选取2016年2月~2019年2月期间我院收治的103例冠心病伴UAP患者，采用乱数表法将其分为研究组（n=52）和对照组(n=51),对照组给予阿托伐他汀联合氯吡格雷治疗,研究组给予阿托伐他汀联合替格瑞洛治疗,比较两组临床疗效、炎性因子、血脂、心绞痛发作情况及不良心脏事件。**结果:**研究组治疗1个月后的临床疗效为88.46%(46/52),高于对照组的66.67%(34/51)(P<0.05)。两组治疗1个月后总胆固醇(TC)、超敏-C反应蛋白(hs-CRP)、三酰甘油(TG)、白介素-6(IL-6)、低密度脂蛋白胆固醇(LDL-C)、心绞痛发作次数、肿瘤坏死因子-α(TNF-α)、心绞痛持续时间均降低,而高密度脂蛋白胆固醇(HDL-C)升高(P<0.05),研究组治疗1个月后TC、TG、LDL-C、IL-6、hs-CRP、TNF-α、心绞痛发作次数、心绞痛持续时间低于对照组,而HDL-C则高于对照组(P<0.05)。两组不良心脏事件发生率比较差异无统计学意义(P>0.05)。**结论:**阿托伐他汀联合替格瑞洛治疗冠心病伴UAP患者,疗效确切,可有效改善其炎性因子、血脂水平,且不增加不良心脏事件发生率,临床应用价值较高。

关键词:阿托伐他汀;替格瑞洛;冠心病不稳定型心绞痛;炎性因子;不良心脏事件;血脂

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Effects of Atorvastatin Combined with Tegrilol on Inflammatory Factors, Blood Lipids and Adverse Cardiac Events in Patients with Unstable Angina Pectoris of Coronary Heart Disease*

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ABSTRACT Objective: To investigate the effects of Atorvastatin Combined with tegrilol on inflammatory factors, blood lipids and adverse cardiac events in patients with unstable angina pectoris (UAP). **Methods:** 103 patients with coronary heart disease and UAP who were admitted to our hospital from February 2016 to February 2019 were selected, they were randomly divided into study group (n=52), control group (n=51). The control group was treated with Atorvastatin Combined with clopidogrel, and the study group was treated with Atorvastatin Combined with clopidogrel. The clinical efficacy, inflammatory factors, blood lipids, angina pectoris and adverse cardiac events were compared between the two groups. **Results:** The clinical efficacy of the study group was 88.46% (46/52) after one month of treatment, which was higher than 66.67% (34/51) of the control group (P<0.05). One month after treatment, total cholesterol (TC), hypersensitive C-reactive protein (hs-CRP), triglyceride (TG), interleukin-6 (IL-6), low density lipoprotein cholesterol (LDL-C), frequency of angina attack, tumor necrosis factor-α (TNF-α) and duration of angina pectoris in both groups decreased, while high density lipoprotein cholesterol (HDL-C) decreased. The TC, TG, LDL-C, IL-6, hs-CRP, TNF-α, angina attack times and duration of angina in the study group were lower than those in the control group one month after treatment, while HDL-C was higher than those in the control group (P<0.05). There was no significant difference in the incidence of adverse cardiac events between the two groups (P>0.05). **Conclusion:** Atorvastatin combined with Tiglillo is effective in the treatment of UAP patients with coronary heart disease. It can effectively improve the levels of inflammatory factors and blood lipids without increasing the incidence of adverse cardiac events, and has high clinical value.

Key words: Atorvastatin; Tegrilol; Unstable angina pectoris of coronary heart disease; Inflammatory factors; Adverse cardiac events; Lipid

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前言

冠心病是指冠状动脉血管产生动脉粥样硬化病变,引起血

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管痉挛和局部血栓形成,致使冠状动脉供血范围内的心肌发生缺血性坏死,最终影响心脏功能的一类心脏病[1-3]。不稳定型心绞痛(UAP)则是冠心病的常见并发症之一,临床主要表现为心绞痛,且患者在夜间疼痛时间较长,若未能及时予以治疗,可发展至急性心肌梗塞,威胁患者性命[4,5]。现临床针对冠心病伴UAP的治疗尚无统一方案,主要采用抗血小板药物、硝酸酯类药物、抗凝血酶药物、钙拮抗剂、β受体阻滞剂等,其中以氯吡格雷联合阿托伐他汀较为常见[6,7],但不少临床实践证实氯吡格雷与二磷酸腺苷受体的结合具有不可逆性,且易增加出血风险[8]。替格瑞洛是新型的二磷酸腺苷受体拮抗剂,抗血小板能力强,起效快,疗效稳定[9]。本研究通过对我院收治的部分冠心病伴UAP患者给予阿托伐他汀联合替格瑞洛治疗,疗效显著,整理报道如下。

1 资料与方法

1.1 一般资料

选取我院于2016年2月~2019年2月期间收治的冠心病伴UAP患者103例,本次研究已获取我院伦理学委员会批准进行。纳入标准:(1)冠心病诊断标准参考美国心脏病协会制定的相关标准[10],UAP诊断标准参考《2007年中国不稳定性心绞痛和非ST段抬高心肌梗死诊断与治疗指南》制定的相关标准[11];(2)临床表现为阵发性胸痛,静息心电图均出现2个或2个以上的的相邻导联ST段下移≥0.1 mV;(3)均经冠状动脉造影确诊;(4)知情本研究且签署了同意书。排除标准:(1)合并肝肾功能不全者;(2)恶性心律失常、重度心功能不全、高血压急症者;(3)合并自身免疫性疾病、恶性肿瘤者;(4)妊娠及哺乳期妇女;(5)慢性传染性疾病者;(6)未能完成本次研究,中途退出治疗者;(7)对本次用药存在过敏者。根据随机数表法将患者分为研究组(n=52)、对照组(n=51),其中对照组男31例,女20例,年龄42~80岁,平均(52.94± 4.38)岁;病程2~7年,平均(4.19± 0.82)年;体质量指数20.3~26.2 kg/m^2,平均(23.18± 1.02)kg/m^2。研究组男33例,女19例,年龄43~80岁,平均(53.18± 3.92)岁;病程2~8年,平均(4.26± 0.93)年;体质量指数20.9~25.8 kg/m^2,平均(23.26± 0.97)kg/m^2。两组一般资料对比未见差异(P>0.05)。

1.2 方法

入院后均嘱咐其卧床休息、合理营养膳食等,同时给予硝酸酯类药物、β受体阻滞剂及钙离子拮抗剂等药物治疗。在此基础上,对照组给予赛诺菲(杭州)制药有限公司生产的硫酸氢氯吡格雷片(国药准字H20056410,规格:75 mg)治疗,首剂量300 mg/次,之后75 mg/次,口服,1次/d,同时给予北京嘉林公司生产的阿托伐他汀钙片(国药准字:H20093819,规格:20 mg)治疗,10 mg/次,口服,1次/d。研究组则给予阿托伐他汀联合替格瑞洛(阿司利康公司,国药准字:J20130020,规格:90 mg),阿托伐他汀治疗方法同对照组,替格瑞洛首剂量180 mg/次,之后90 mg/次,2次/d。两组均连续治疗1个月。

1.3 观察指标

1.3.1 临床疗效 记录两组治疗1个月后的临床疗效。参考《心血管系统药物临床研究指导原则》[12],显效:硝酸甘油用量或心绞痛发作次数减少80%以上,心电图缺血性ST段基本正常;有效:心电图缺血性ST段回升>0.05 mV,但未达到正常,主要导联倒置T波变浅超过25%,或T波由平坦变为直立,硝酸甘油用量或心绞痛发作次数减少50%~80%;无效:硝酸甘油用量或心绞痛发作次数减少<50%,静息心电图未见改善。总有效率=显效率+有效率。

1.3.2 心绞痛情况 记录两组心绞痛发作频率及持续时间,记录时间为治疗前、治疗1个月后。

1.3.3 炎性因子、血脂检测 抽取患者治疗前、治疗1个月后的清晨空腹静脉血4 mL,经离心半径18 cm,4300 r/min离心12 min,取上清,置于-30℃冰箱中待测。血清白介素-6(IL-6)、超敏-C反应蛋白(hs-CRP)、肿瘤坏死因子-α(TNF-α)水平经酶联免疫吸附试验检测,血清总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)及高密度脂蛋白胆固醇(HDL-C)水平经双试剂酶法检测,严格遵守试剂盒(深圳晶美生物工程有限公司)说明书进行操作。

1.3.4 不良心脏事件 记录治疗期间引起的不良心脏事件发生情况。

1.4 统计学方法

采用SPSS25.0进行统计分析,计量资料以($\bar{x}\pm s$)表示,采用t检验,计数资料以率(%)表示,采用x^2检验,以α=0.05为检验标准。

2 结果

2.1 疗效比较

治疗1个月后,研究组的临床疗效为88.46%(46/52),高于对照组的66.67%(34/51)(P<0.05),详见表1。

表1 疗效比较[n(%)]

Table 1 Comparison of efficacy [n(%)]

Groups	Markedly effective	Effective	Invalid	Total effective rate
Control group(n=51)	13(25.49)	21(41.18)	17(33.33)	34(66.67)
Study group(n=52)	19(36.54)	27(51.92)	6(11.54)	46(88.46)
x^2				7.052
P				0.008

2.2 血脂指标比较

两组治疗前血清TC、TG、LDL-C、HDL-C比较无差异(P>0.05);两组治疗1个月后TC、TG、LDL-C均降低,而HDL-C升高(P<0.05);研究组治疗1个月后TC、TG、LDL-C低于对照组,而HDL-C则高于对照组(P<0.05);详见表2。

表 2 血脂指标比较($\bar{x}\pm s$)

Table 2 Comparison of blood lipid indices($\bar{x}\pm s$)

Groups	TC(mmol/L)		TG(mmol/L)		LDL-C(mmol/L)		HDL-C(mmol/L)	
	Before treatment	One month after treatment	Before treatment	One month after treatment	Before treatment	One month after treatment	Before treatment	One month after treatment
Control group (n=51)	6.29± 0.75	4.23± 0.63[a]	3.03± 0.26	1.99± 0.32[a]	5.19± 0.35	3.15± 0.41[a]	1.26± 0.28	2.02± 0.33[a]
Study group (n=52)	6.33± 0.82	2.64± 0.49[a]	2.98± 0.31	1.08± 0.25[a]	5.17± 0.24	1.64± 0.37[a]	1.34± 0.39	3.20± 0.41[a]
t	0.258	14.313	0.886	16.100	0.339	19.630	1.194	16.072
P	0.797	0.000	0.378	0.000	0.735	0.000	0.235	0.000

Note: Compared with before treatment, [a]*P*<0.05.

2.3 炎性因子指标比较

两组治疗前血清 IL-6、hs-CRP、TNF-α 水平比较无差异（*P*>0.05）；治疗 1 个月后，两组上述炎性因子水平均降低，且研究组低于对照组（*P*<0.05）；详见表 3。

表 3 炎性因子比较($\bar{x}\pm s$)

Table 3 Comparison of inflammatory factors($\bar{x}\pm s$)

Groups	IL-6(pg/mL)		hs-CRP(mg/L)		TNF-α(ng/mL)	
	Before treatment	One month after treatment	Before treatment	One month after treatment	Before treatment	One month after treatment
Control group(n=51)	30.15± 7.59	22.13± 6.33[a]	9.91± 1.24	6.38± 0.91[a]	5.97± 0.29	4.62± 0.91[a]
Study group(n=52)	30.12± 8.43	13.04± 5.25[a]	9.87± 1.37	4.37± 0.74[a]	6.01± 0.37	3.15± 0.78[a]
t	0.019	7.939	0.155	12.310	0.676	8.808
P	0.985	0.000	0.877	0.000	0.501	0.000

Note: Compared with before treatment, [a]*P*<0.05.

2.4 心绞痛发作情况比较

两组治疗前心绞痛发作次数、心绞痛持续时间比较无差异（*P*>0.05）；两组治疗 1 个月后心绞痛发作次数及持续时间均下降，且研究组低于对照组（*P*<0.05）；详见表 4。

表 4 心绞痛发作情况比较($\bar{x}\pm s$)

Table 4 Comparison of angina attacks($\bar{x}\pm s$)

Groups	Number of attacks of angina pectoris(times/weeks)		Duration of angina pectoris(min)	
	Before treatment	One month after treatment	Before treatment	One month after treatment
Control group(n=51)	9.43± 1.52	5.72± 1.19[a]	8.65± 1.32	2.75± 0.46[a]
Study group(n=52)	9.48± 1.45	2.76± 0.82[a]	8.61± 1.47	1.06± 0.29[a]
t	0.171	14.724	0.145	22.350
P	0.865	0.000	0.885	0.000

Note: Compared with before treatment, [a]*P*<0.05.

2.5 不良心脏事件比较

治疗期间，对照组发生 1 例缺血性卒中、2 例急性心肌梗死，不良心脏事件发生率为 5.88%(3/51)；研究组用药期间发生 1 例缺血性卒中、1 例急性心肌梗死，不良心脏事件发生率为 3.85%(2/52)；两组不良心脏事件发生率比较差异无统计学意义（x^2=0.414，*P*=0.634）。

3 讨论

近年来随着人们生活水平的改善，高脂高盐等不良饮食习惯的增加，导致冠心病的发生风险呈逐年递增趋势[13]。以往大量研究证实[14-16]，炎性反应和血脂代谢异常可导致心血管系统产生慢性病变，同时其还是冠状动脉粥样硬化发生的危险因素之一。UAP 作为急性冠脉综合征的一种类型，其主要发病机制为冠状动脉出现不稳定型粥样硬化斑块，而斑块脱落、破裂后引起的出血和栓塞现象，可导致冠状动脉狭窄或痉挛，最终引起心肌细胞缺血缺氧，临床表现为阵发性胸痛等症状[17-19]。由此可见，血脂和炎性因子与 UAP 的病情进展关系密切。目前临床有关冠心病伴 UAP 的治疗方案较多，但大多数药物的主要作用为缓解患者临床症状，在药物的选择方面应对其降脂、减轻血管内皮细胞炎性反应、降低血小板聚集等方面给予重视[20,21]。

氯吡格雷联合阿托伐他汀的治疗虽有一定效果,但仍有不少患者停药后极易复发,且不良心脏事件发生率较高。替格瑞洛于2011年在美国上市后,被不少临床指导机构推荐为急性冠脉综合征的常用药物之一,并于2012年获批进入中国。替格瑞洛在人体内不需经过肝脏代谢激活,故而其具有强效、快速及可逆性抑制血小板等特点[22,23]。

本次研究结果中,研究组治疗1个月后的临床疗效、心绞痛发作改善情况均优于对照组,可见阿托伐他汀联合替格瑞洛治疗冠心病伴UAP,可进一步提高治疗效果。究其原因,阿托伐他汀是第二代羟甲基戊二酸单酰辅酶A的还原酶抑制剂,具有亲水性,易被人体吸收,且其半衰期较长,可发挥较强的调脂、抗炎效果[24]。替格瑞洛为非前体药物,可避免肝脏对药物作用的影响,减少机体的进一步损伤。此外既往亦有研究证实[25],抗血小板药物在抑制血小板的同时,还可抑制因血小板聚集所引起的心肌细胞损伤,发挥间接的修复和保护心肌的效果。替格瑞洛具有极强的抑制血小板聚集能力,与氯吡格雷相比,可起到更好的血管、心肌修复的作用,改善心绞痛发作情况。既往研究结果表明[26],多数冠心病患者中均存在HDL-C水平低于参考范围,而TC、TG、LDL-C水平则高于参考范围的情况。另也有研究表明[27],炎性因子如IL-6、hs-CRP、TNF-α均在冠心病伴UAP患者的病情进展中发挥重要作用。本研究中两组患者血脂、炎性因子水平均有所改善,且阿托伐他汀联合替格瑞洛治疗者改善效果更佳,分析其原因,阿托伐他汀不仅可稳定动脉粥样硬化,还可调节血脂水平恢复正常,联合替格瑞洛治疗后,替格瑞洛可减少阿托伐他汀的代谢而提高其调节血脂能力[28]。以往研究表明[29]血小板和血小板-单核细胞的相互作用在炎症中扮演了重要角色,而替格瑞洛的抗炎效应可能是通过抑制血小板-中性粒细胞聚集和血小板脱落CD40L来发挥作用。此外,本研究中研究组的不良心脏事件发生率虽低于对照组,但经统计学比较无差异。邢寻静等人[30]的研究表明,阿托伐他汀联合替格瑞洛治疗冠心病伴UAP可有效降低不良心脏事件发生风险。这与本次研究结果存在一定差异,可能与本次研究样本量偏少,导致结果存在一定的偏倚有关。后续将扩大样本量,严格控制筛选标准,以期获得更为准确的数据。

阿托伐他汀联合替格瑞洛治疗冠心病伴UAP患者,疗效确切,可有效改善其炎性因子、血脂水平,安全性较好,具有一定的临床应用价值。

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