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阿托伐他汀钙片治疗脑梗死的疗效及其对 MMP-2 表达的影响 *

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摘要 目的：探讨阿托伐他汀钙片治疗脑梗死的疗效及其对基质金属蛋白酶(MMP-2)表达的影响。**方法：**选择 2019 年 5 月 -2021 年 2 月在本院诊治的脑梗死患者 64 例，根据随机信封抽签原则将患者分为阿托伐他汀组 32 例与对照组 32 例。对照组给予常规双抗治疗，阿托伐他汀组以对照组为基础给予阿托伐他汀治疗，两组都治疗观察 3 个月，记录 MMP-2 表达的变化。**结果：**治疗后阿托伐他汀组的总有效率为 93.8 %，高于对照组的 68.8 %(P<0.05)。两组治疗后的低密度脂蛋白胆固醇（LDL-C）、甘油三酯(TG)、总胆固醇(TC)水平均低于治疗前(P<0.05)，高密度脂蛋白胆固醇(HDL-C)水平高于治疗前(P<0.05)，组间对比无差异(P>0.05)。两组治疗后的大脑中动脉平均血流速度(Vm)明显高于治疗前，搏动指数(PI)明显低于治疗前，阿托伐他汀组与对照组对比差异明显(P<0.05)。两组治疗后的血清 MMP-2 含量低于治疗前，阿托伐他汀组低于对照组(P<0.05)。两组治疗期间的不良反应主要为恶心呕吐、低血压、静脉血栓、头晕脑胀，组内对比无差异(P>0.05)。**结论：**阿托伐他汀治疗脑梗死能降低 MMP-2 水平，可在平衡血脂水平的基础上提高患者的治疗效果，还可提高大脑中动脉的血流速度，且为增加不良反应。

关键词：阿托伐他汀；脑梗死；基质金属蛋白酶 -2

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Efficacy of Atorvastatin Calcium Tablets in the Treatment of Cerebral Infarction and Its Effect on the Expression of MMP-2*

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ABSTRACT Objective: To investigate the efficacy of atorvastatin calcium tablets in the treatment of cerebral infarction and its effect on the expression of matrix metallo protease (MMP)-2. **Methods:** From May 2019 to February 2021, A total of 64 cases of patients with cerebral infarction who were diagnosed and treated in our hospital were selected. All the cases were divided into atorvastatin group with 32 cases and matched group with 32 cases in each groups accorded to the principle of random envelope drawing. The matched group were given conventional dual-antibody therapy, and the atorvastatin group were given atorvastatin treatment on the basis of the treatment of the matched group. Both groups were treated for 3 months, and the changes of MMP-2 expression were recorded. **Results:** Post-treatment, the total effective rates in the atorvastatin group were 93.8 %, which were higher than that in the matched group (68.8 %) (P<0.05). The levels of low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol (TC) post-treatment in both groups were lower than those pretherapy, the level of low-density lipoprotein cholesterol (HDL-C) were higher than that pretherapy, and there were no difference compared between the groups (P>0.05). The mean blood flow velocity (Vm) of the middle cerebral artery in the two groups post-treatment were higher than that pretherapy, and the pulsatility index (PI) were lower than that pretherapy, compared with the matched group, the difference were also significant (P<0.05). The levels of serum MMP-2 in the two groups post-treatment were lower than those pretherapy, and those in the atorvastatin group were lower than those in the matched group (P<0.05). The main adverse reactions during treatment in the two groups were nausea and vomiting, hypotension, venous thrombosis, dizziness and brain swelling, and there were no significant difference compared between the two groups (P<0.05). **Conclusion:** Atorvastatin in the treatment of cerebral infarction can reduce the level of MMP-2, improve the therapeutic effect of patients on the basis of balancing the blood lipid level, and also increase the blood flow velocity of the middle cerebral artery without increasing the occurrence of adverse reactions.

Key words: Atorvastatin; Cerebral infarction; Matrix metalloproteinase-2

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前言

脑梗死在我国具有较高的三高＂发病率高、致残率高、复发率高＂等特点，严重威胁身心健康，并为患者家庭带来沉重负担[1,2]。颈动脉粥样硬化是脑梗死发生的病理基础，颈动脉粥样硬化可导致颈动脉血流速度减慢，导致斑块破裂甚或新血管生成，从而诱发血栓形成[3]。血脂异常是颈动脉粥样硬化的主要发病因素，有效降低血脂及炎性因子水平，稳定、缩小脑动脉硬化斑块，可有效改善患者预后[4]。阿托伐他汀作为羟甲基戊二酸单酰辅酶 A（Hydroxymethylglutaryl-CoA, HMG-CoA）还原酶的抑制剂，具有很好的降脂作用，可降低机体的低密度脂蛋白胆固醇（Low density lipoprotein cholesterol, LDL-C）和总胆固醇（Total cholesterol, TC）水平，降低脑动脉硬化风险[5,6]。阿托伐他汀除具有良好的调脂作用外，还可促进新生血管及神经细胞的再生，具有抗炎、抗栓作用，可增加脑血流再灌注，减少自由基，改善患者预后[7,8]。现代研究表明基质金属蛋白酶（Matrixmetalloprotease, MMP）可参与脑梗死的发生与发展，特别是其破坏导致血管的完整性损伤，从而导致血管内皮细胞细胞外基质降解[9]。本文具体探讨了阿托伐他汀钙片治疗脑梗死的疗效及其对 MMP-2 表达的影响，以明确阿托伐他汀的作用效果与作用机制。

1 资料与方法

1.1 研究对象

2019 年 5 月 -2021 年 2 月选择本院诊治的脑梗死患者 64 例作为研究对象。

纳入标准：经 CT 或 MRI 检查证实为脑梗死；颈动脉超声检查发现颈动脉粥样硬化；年龄 30-70 岁；入院前 6 个月未使用他汀类药物治疗者；患者均签署知情同意书；医院伦理委员会批准了此次研究。

排除标准：严重心脏、肝脏、肾脏功能不全者；创伤性脑血管疾病患者；未按规定服药及资料不全者；入组前已参加其他研究。

根据随机信封抽签原则把患者分为阿托伐他汀组 32 例与对照组 32 例，两组一般资料对比无差异（P>0.05）。见表 1。

表 1 一般资料比较

Table 1 Comparison of the general data

Indexs	Matched group (n=32)	The atorvastatin group(n=32)
Gender(male/female)	16/16	17/15
Disease course/(month)	1.89± 0.26	1.80± 0.86
Age/(Year)	59.63± 4.36	58.13± 10.25
Fasting blood glucose/(mmol/L)	5.48± 0.92	5.50± 0.45
Body mass index/(kg/m^2)	22.89± 3.65	23.00± 4.00
Systolic pressure /(mmHg)	124.76± 10.84	122.82± 10.90
Diastolic pressure/(mmHg)	81.54± 0.77	81.50± 0.79

1.2 治疗方法

对照组：给予常规治疗，阿司匹林肠溶片（拜阿司匹灵，拜耳医药保健有限公司，进口药品注册证号：H20160684，国药准字 J20171021）100 mg，口服，1 次 /d；硫酸氢氯吡格雷片（波立维，赛诺菲制药有限公司，进口药品注册证号：H20171237，国药准字 J20180029）75 mg，口服，1 次 /d。阿司匹林肠溶片 100 mg+ 硫酸氢氯吡格雷片 75 mg 双抗治疗 21 天，之后阿司匹林肠溶片继续治疗，治疗观察 3 个月；

阿托伐他汀组：以对照组为基础，给予阿托伐他汀钙片治疗，阿托伐他汀钙片（乐普制药科技有限公司，国药准字 H20163270）20 mg，口服，1 次 /d，治疗观察 3 个月。

1.3 观察指标

（1）采用美国国立卫生研究院卒中量表判定临床疗效，分为基本治愈、显著进步、进步与无效四个级别，（基本治愈 + 显著进步）/ 组内例数× 100.0 %= 总有效率。

（2）抽取两组治疗前后禁食 8 h 以上的清晨肘静脉血 6 mL，采用生化分析仪测定 LDL-C、甘油三酯（Triglycerides, TG）、TC、高密度脂蛋白胆固醇（High density lipoprotein cholesterol, HDL-C）等指标。

（3）所有患者在治疗前后经颅多普勒超声检测仪检测患者的大脑中动脉的血流动力学，取样为色彩最饱和处，记录平均血流速度（Vm）和搏动指数（Pulsatility index, PI）。

（4）取上述的血液学指标，2000 r/min 离心 10 min，取上层血清，采用酶联免疫法（上海生工公司）测定 MMP-2 含量。

（5）观察与记录所有患者在治疗期间出现的不良反应情况，包括恶心呕吐、低血压、静脉血栓、头晕脑胀等。

1.4 统计学处理

应用 SPSS 22.00 进行统计分析，检验水准 α=0.05，P<0.05 代表对比差异有统计学意义。计量数据以（$\bar{x}\pm s$）表示，计数资料采用 n%表示，对比采用 t 检验与卡方 x^2 检验分析等。

2 结果

2.1 总有效率对比

治疗后阿托伐他汀组的总有效率较对照组高（P<0.05）。见表 2。

2.2 血脂指标变化对比

两组治疗后的 LDL-C、TG、TC 水平均较治疗前低，HDL-C 水平较治疗前高（P<0.05），组间对比无差异（P>0.05）。见表 3。

表 2 两组治疗后总有效率对比(n)

Table 2 Comparison of total response rate post-treatment between the two groups (n)

Groups	n	Basic cure	Marked improvement	Advance	Invalid	Total effective rate
Matched group	32	12	10	7	3	22(68.8%)*
The atorvastatin group	32	22	8	2	0	30(93.8%)

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

表 3 治疗前后血脂指标变化对比(mmol/L,均数± 标准差)

Table 3 Comparison of blood lipid indexes pretherapy and post-treatment (mmol/L, mean ± standard deviation)

Groups	n	LDL-C		HDL-C		TG		TC	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Matched group	32	3.55± 0.28	2.64± 0.31#	1.18± 0.34	1.64± 0.26#	2.09± 0.16	0.99± 0.21#	5.22± 0.13	4.43± 0.26#
The atorvastatin group	32	3.51± 0.31	2.68± 0.41#	1.19± 0.15	1.62± 0.26#	2.11± 0.14	0.91± 0.13#	5.19± 0.27	4.44± 0.31#

Note: Compared with pretherapy, #P<0.05, the same below.

2.3 脑血流动力学变化对比

两组治疗后的大脑中动脉 Vm 明显高于治疗前,PI 明显较治疗前低,阿托伐他汀组与对照组对比差异明显(P<0.05)。见表 4。

表 4 两组治疗前后脑血流动力学变化对比(均数± 标准差)

Table 4 Comparison of cerebral hemodynamic changes pretherapy and post-treatment (mean ± standard deviation)

Groups	n	Vm(cm/s)		PI	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Matched group	32	46.83± 5.69	59.28± 7.01#	0.94± 0.11	0.78± 0.10#
The atorvastatin group	32	46.10± 5.10	52.76± 8.74#*	0.94± 0.12	0.84± 0.11#*

2.4 MMP-2 含量对比

两组治疗后的血清 MMP-2 含量明显低于治疗前，阿托伐他汀组明显低于对照组(P<0.05)。见表 5。

表 5 治疗前后 MMP-2 含量变化对比(ng/mL,均数± 标准差)

Table 5 Comparison of MMP-2 content pretherapy and post-treatment (ng/mL, mean ± standard deviation)

Groups	n	Pretherapy	Post-treatment
Matched group	32	210.87± 36.30	142.45± 23.09#
The atorvastatin group	32	210.98± 29.11	76.30± 10.44#*

2.5 不良反应情况对比

两组治疗期间的不良反应主要为恶心呕吐、低血压、静脉血栓、头晕脑胀,组内对比无差异(P>0.05)。见表 6。

表 6 治疗期间不良反应情况对比(n)

Table 6 Comparison of adverse effects during the (n)

Groups	n	Nausea and vomitting	Hypopiesia	Venous thrombus	Dizziness brain distension
Matched group	32	2(6.3%)	1(3.1%)	0(0.0%)	1(3.1%)
The atorvastatin group	32	3(9.4%)	1(3.1%)	1(3.1%)	2(6.3%)

3 讨论

脑梗死主要由颈动脉粥样硬化引起,当前在国内外的发病人数逐年增加[10]。研究发现脑梗死的病灶可被分为缺血中心区和其周围的缺血半暗带,二者是一个动态转换的过程,与缺血程度、时间息息相关,随着脑梗死的加重和脑梗死时间的持续

延长,均会造成缺血半暗带进一步缩小以及中心坏死区的进一步扩大[11-13]。缺血中心区的损害虽是不可逆的,但缺血中心区的缺血半暗带的损害是可逆的,这也为康复临床治疗提供了理论基础[14]。血脂异常是脑梗死发生的重要因素,特别是在动脉粥样硬化的形成过程中,血脂紊乱可导致血管内皮损伤及内皮功能紊乱[15]。阿司匹林等为脑梗死的常规治疗药物,可抑制血管平滑肌细胞增殖,也可抑制血小板聚集,进而抗血栓形成[16]。

本研究显示治疗后阿托伐他汀组较对照组高;两组治疗后的 LDL-C、TG、TC 水平均低于治疗前,HDL-C 水平高于治疗前,组间对比无差异;两组治疗期间的不良反应主要为恶心呕吐、低血压、静脉血栓、头晕脑胀,组内对比无差异,表明阿托伐他汀的应用可在平衡血脂水平的基础上提高患者的治疗效果,且在临床上的应用具有很好的安全性。该结果与 Chen J[17]的报道具有一致性。分析可知:脂质代谢异常是动脉硬化产生的重要因素,脂质代谢紊乱与脑血管病关系密切。TG、TC 可导致动脉粥样硬化、管腔狭窄、斑块形成并脱落,最终导致心脑血管事件发生;HDL-C、LDL-C 是血脂与动脉粥样硬化关系的主要因子,与动脉粥样硬化斑块稳定性息息相关。阿托伐他汀可抑制 HMG-CoA 活性,降低血清 LDL-C 合成,上调 HDL-C 水平,最小程度的减少对患者体内血管的损害;其也能通过增强清除氧自由基的作用来降低动脉粥样硬化形成、保护血管内皮与稳定易损斑块,进而控制血脂,提高疗效,且具有较低的不良反应[18,19];两组治疗后的大脑中动脉 Vm 明显高于治疗前,PI 明显低于治疗前,阿托伐他汀组与对照组对比差异明显。该结果与赵雪艳[20]的报道具有一致性。分析可知,脑梗死的发生与发展是由凝血系统功能障碍,血液高凝状态可使得机体纤维蛋白的溶解能力下降,使血小板被激活,在血动脉管壁下粘附[21]。PI 可反映被检血管的顺应性、弹性、阻力,是一个综合反映心动周期内血流速度的参数。Vm 可反映出被检血管的血流情况,指心动周期末心室舒张末期的最高血流速度[22,23]。阿托伐他汀使机体的血红细胞聚集性、血浓度降低,从而可提高大脑中动脉的平均血流速度。且该药物可增加颈部血管的血流量,使血管平滑肌细胞和内皮细胞钙离子含量增多,发挥扩张血管、调节血管张力的作用[24]。同时阿托伐他汀有利于凝血功能的改善,影响机体内皮细胞的功能、交感与副交感神经系统的兴奋性,从而促进改善患者的预后[25];两组治疗后的血清 MMP-2 含量较治疗前低,阿托伐他汀组较对照组低,表明阿托伐他汀的应用抑制 MMP-2 的释放。该结果与 Sakurai K[26]的报道具有一致性。分析可知,MMPs 是一类蛋白酶超家族,对细胞外基质具有降解活性,可作用于Ⅳ型明胶、层黏蛋白、纤黏蛋白等,可削弱斑块的强度,降解斑块的细胞外基质成分,从而影响患者的预后[27,28]。MMP-2 可降低细胞外基质,破坏脑血管的完整性,特异性降解 I、II 型胶原,进而加重血脑屏障损害。当患者引发脑梗死时,脑组织损伤、氧化应激反应及炎症因子的大量表达均会刺激内皮细胞等,进而激活 MMP 系统,进一步大量表达 MMP-2。阿托伐他汀可通过改善内皮功能,抑制炎症反应,从而起到稳定动脉粥样硬化斑块的作用;也可促进血管内皮一氧化氮释放、降低脂质沉积,从而改善脑梗死患者的预后[29,30]。但本研究由于受到经费因素的影响,样本量较小,未进行长期随访,分组也较少,确切结论尚需进一步研究证实。

总之,阿托伐他汀治疗脑梗死能降低 MMP-2 水平,可在平衡血脂水平的基础上提高患者的治疗效果,还可提高大脑中动脉的血流速度,且不会增加不良反应。

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