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阿托伐他汀强化降脂治疗急性脑梗死的疗效及对 TNF-α、IL-10、IL-18、MMP-9 水平的影响 *

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摘要 目的：探讨阿托伐他汀强化降脂治疗急性脑梗死（ACI）的临床疗效，并分析其对肿瘤坏死因子 -α（TNF-α）、白细胞介素 -10（IL-10）、白细胞介素 -18（IL-18）及基质金属蛋白酶 -9（MMP-9）水平的影响。**方法**：选取 2015 年 3 月 -2016 年 12 月我院收治的 82 例 ACI 患者，采用随机数字表法随机分为强化组（n=41）与常规组（n=41）。在常规治疗的基础上，常规组患者给予 20 mg/ 次的阿托伐他汀治疗，强化组患者给予 40 mg/ 次的阿托伐他汀治疗，两组均连续治疗 8w。治疗结束后对比两组患者的临床疗效，对比两组患者治疗前后总胆固醇（TC）、三酰甘油（TG）、高密度脂蛋白胆固醇（HDL-C）、低密度脂蛋白胆固醇（LDL-C）、组织型纤溶酶原激活物（t-PA）、血浆纤溶酶原激活物抑制剂 -1（PAI-1）、血浆纤维蛋白原（FIB）、TNF-α、IL-10、IL-18、MMP-9 水平。**结果**：强化组与常规组患者的总有效率分别为 95.12%、80.49%，与常规组对比，强化组患者的临床总有效率明显升高（*P<0.05*）；两组患者治疗后的 TC、TG、LDL-C、PAI-1、FIB、TNF-α、IL-18、MMP-9 水平均较治疗前显著降低，HDL-C、t-PA、IL-10 水平均显著升高（*P<0.05*），且治疗后强化组患者的 TC、TG、LDL-C、PAI-1、FIB、TNF-α、IL-18、MMP-9 水平均低于常规组，HDL-C、t-PA、IL-10 均高于常规组（*P<0.05*）。**结论**：阿托伐他汀强化降脂治疗 ACI 疗效较好，能够显著改善患者血脂、纤溶系统及炎症因子相关指标水平，具有降脂、调节纤溶活性及抑制炎症的作用。

关键词：急性脑梗死；阿托伐他汀；强化降脂；临床疗效；炎症因子；基质金属蛋白酶

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Effect of Atorvastatin Intensive Lipid-Lowering Therapy on Acute Cerebral Infarction and its Effect on Levels of TNF-α, IL-10, IL-18, MMP-9*

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ABSTRACT Objective: To investigate the clinical efficacy of atorvastatin intensive lipid-lowering therapy on patients with acute cerebral infarction, and to analyze the effects on levels of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), interleukin-18 (IL-18) and matrix metalloproteinase-9 (MMP). **Methods:** Selected 82 patients with ACI who were treated in our hospital from March 2015 to December 2016,and they were randomly divided intensive group (n=41) and conventional group (n=41). On the basis of conventional treatment, patients in the conventional group were treated with atorvastatin 20 mg/times, patients in intensive group were treated with atorvastatin 40 mg/times, and the two groups were treated with continuous 8w. Compared the clinical efficacy of two groups after treatment, and the levels of total cholesterol (TC), three glycerol (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), tissue type plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), plasma fibrinogen (FIB), TNF-α, IL-10, IL-18, MMP-9 in two group before and after treatment. **Results:** The total effective rates of the intensive group and the conventional group were 95.12% and 80.49% respectively, compared with the conventional group, the total effective rate of the patients in the intensive group was significantly increased (*P<0.05*). The levels of TC, TG, LDL-C, PAI-1, FIB, TNF-α, IL-18, MMP-9 in the two groups after treatment were significantly lower than those before treatment, the levels of HDL-C, t-PA and IL-10 were increased significantly (*P<0.05*). After treatment, the levels of TC, TG, LDL-C, PAI-1, FIB, TNF-α, IL-18, MMP-9 in the intensive group were lower than those in the conventional group, and the levels of HDL-C, t-PA and IL-10 were higher than those of the conventional group (*P<0.05*). **Conclusion:** The curative effect of atorvastatin intensive lipid-lowering in treatment of ACI is better, and it can significantly improve the level of blood lipids, fibrinolytic system and inflammatory factors, which has the effects of lowering blood fat, regulating fibrinolytic activity and inhibiting inflammation.

Key words: Acute cerebral infarction; Atorvastatin; Intensive lipid-lowering; Clinical efficacy; Inflammatory factor; Matrix metalloproteinase

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急性脑梗死(ACI)是一种常见的神经内科急症,是由于患者脑部动脉管腔狭窄或者闭塞造成脑组织缺血并引起坏死,从而导致患者脑功能障碍的缺血性脑血管疾病,常发于中老年群体,在临床上具有较高的发病率,严重威胁了中老年人的生命健康[1,2]。相关研究显示[3-5],动脉粥样硬化斑块溃疡形成或者突然破裂是引发 ACI 的重要原因,长期的动脉粥样硬化易引发炎症及损伤处血小板聚集,从而形成局部血栓,因此有报道认为炎性因子所介导的炎症反应及炎症损伤在该病的发生与发展中也发挥着重要作用。同时有报道称[6],基质金属蛋白酶(MMP)也参与了动脉粥样硬化斑块的破裂,是导致斑块不稳定的重要因素之一。目前临床上治疗 ACI 多采用他汀类药物,其中阿托伐他汀是较为常用的他汀类药物,在治疗 ACI 中取得了较好的疗效,但有研究报道不同剂量的阿托伐他汀治疗 ACI 所取得的效果不同[7-8]。本研究旨在探讨不同剂量的阿托伐他汀治疗 ACI 的效果,并分析其对肿瘤坏死因子 -α(TNF-α)、白细胞介素 -10(IL-10)、白细胞介素 -18(IL-18)及基质金属蛋白酶 -9(MMP-9)的影响,以期为 ACI 的治疗提高用药依据,整理报告如下。

1 资料与方法

1.1 一般资料

选取 2015 年 3 月 -2016 年 12 月我院收治的 82 例 ACI 患者为研究对象。纳入标准:均符合中华医学会神经病学分会脑血管病学组制定的中国急性缺血性脑卒中诊治指南中关于 ACI 的诊断标准[9];发病时间均为 24h 内;患者对本研究治疗方案知情,并签署知情同意书。排除标准:对本次研究药物过敏者;合并有严重器质性疾病者;患有恶性肿瘤者。82 例患者按照随机数字表法分为强化组与常规组,各 41 例。强化组患者中男 26 例,女 15 例,年龄 56-79 岁,平均(67.4± 6.3)岁,发病时间为 3-22h,平均(11.3± 3.8)h;常规组患者中男 24 例,女 17 例,年龄 56-78 岁,平均(66.9± 6.1)岁,发病时间为 2-22h,平均(10.9± 3.4)h。两组患者以上数据对比无显著差异(*P>0.05*)。本研究通过医院伦理委员会批准。

1.2 方法

两组患者在入院后均给予控制血压和血糖、吸氧、改善循环、营养神经、抗血小板聚集等常规治疗。常规组口服剂量为 20 mg/ 次的阿托伐他汀钙片(辉瑞制药有限公司生产,国药准字 H20051407,规格:10 mg/ 片)治疗,1 次 /d;强化组口服剂量为 40 mg/ 次的阿托伐他汀治疗,1 次 /d。两组均连续治疗 8w。

1.3 血脂、血清炎性因子等指标水平的检测

在治疗前及治疗 8w 后清晨抽取患者空腹静脉血 3 mL,3000 r/min 离心 10 min,取血清待测,应用美国贝克曼库尔特的 AU5800 全自动生化分析仪检测患者总胆固醇(TC)、三酰甘油(TG)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)等血脂指标。采用酶联免疫吸附法检测 TNF-α、IL-10、IL-18 及 MMP-9 水平,严格按照试剂盒(购自深圳晶美生物工程有限公司)说明书步骤进行操作。纤溶系统相关指标包括组织型纤溶酶原激活物(t-PA)、血浆纤溶酶原激活物抑制剂 -1(PAI-1)、血浆纤维蛋白原(FIB),其中 t-PA 及 PAI-1 应用酶联免疫吸附法检测,严格按照试剂盒(购于上海酶联生物科技有限公司)说明书进行操作;FIB 则应用 FM-16 电脑血浆纤维蛋白原测定仪进行检测。

1.4 疗效判断标准

临床疗效以治疗前后患者神经功能缺损程度评分即美国国立卫生研究所脑卒中评分(NIHSS)[10] 的下降程度为判断标准,痊愈:NIHSS 评分下降程度为 91%-100%;显效:NIHSS 评分评分下降程度为 46%-90%;有效:NIHSS 评分下降程度为 18%-45%;无效:NIHSS 评分下降程度小于 17%。总有效率为痊愈、显效及有效之和的占比。

1.5 观察指标

在治疗 8w 后,根据疗效判定标准评价两组患者的临床疗效,并对比治疗前后两组患者血脂相关指标(TC、TG、HDL-C、LDL-C)、纤溶相关指标(t-PA、PAI-1、FIB)及 TNF-α、IL-10、IL-18、MMP-9 水平变化。

1.6 统计学分析

采用 SPSS19.0 统计学软件对数据进行处理,临床疗效等计数资料均以率的形式表示,采用 x^2 检验,血脂指标水平、纤溶系统相关指标水平以及 TNF-α、IL-10、IL-18、MMP-9 水平等计量资料均以($\bar{x}\pm s$)的形式表示,采用 t 检验,检验标准设置为 α=0.05。

2 结果

2.1 两组临床疗效对比

强化组与常规组患者的总有效率分别为 95.12%、80.49%,与常规组对比,强化组患者的临床总有效率明显更高(*P< 0.05*),见表 1。

表 1 两组临床疗效对比[n(%)]

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

Groups	n	Recovery	Excellent	Effective	Invalid	Total effective rate
Intensive group	41	18(43.90)	13(31.71)	8(19.51)	2(4.88)	39(95.12)
Conventional group	41	13(31.71)	11(26.83)	9(21.95)	8(19.51)	33(80.49)
x^2	-					4.100
P	-					0.043

2.2 两组治疗前后血脂水平变化对比

治疗前两组的各项血脂水平比较无统计学差异(*P>0.05*);与治疗前相比,两组患者治疗后的 TC、TG 及 LDL-C 水平均显著降低,HDL-C 水平显著升高(*P<0.05*),且治疗后强化组患者的 TC、TG 及 LDL-C 水平低于常规组,HDL-C 高于常规组(*P< 0.05*),见表 2。

表 2 两组治疗前后血脂水平变化对比($\bar{x}\pm s$,mmol·L^{-1})

Table 2 Comparison of blood lipid levels between the two groups before and after treatment ($\bar{x}\pm s$, mmol·L^{-1})

Groups	n	Time	TC	TG	HDL-C	LDL-C
Intensive group	41	Before treatment	1.48± 0.32	6.18± 0.65	1.20± 0.26	4.06± 0.69
		After treatment	1.30± 0.25*#	3.90± 0.42*#	1.71± 0.39*#	2.69± 0.32*#
Conventional group	41	Before treatment	1.50± 0.33	6.16± 0.75	1.21± 0.25	4.09± 0.63
		After treatment	1.41± 0.27*	4.43± 0.39*	1.39± 0.31*	3.20± 0.43*

Note: Compared with before treatment, *$P<0.05$, compared with the conventional group after treatment, #$P<0.05$.

2.3 两组治疗前后纤溶系统相关指标水平变化对比

治疗前两组的纤溶系统相关指标水平比较无统计学差异（$P>0.05$）；治疗后，强化组与常规组患者的 t-PA 水平升高，PAI-1、FIB 水平降低（$P<0.05$），且治疗后强化组患者的 t-PA 水平高于治疗后常规组，PAI-1、FIB 水平降低常规组（$P<0.05$），见表 3。

表 3 两组治疗前后纤溶系统相关指标水平变化对比($\bar{x}\pm s$)

Table 3 The changes of fibrinolytic system related indexes before and after treatment in two groups ($\bar{x}\pm s$)

Groups	n	Time	t-PA(IU/L)	PAI-1(ng/mL)	FIB(mg/mL)
Intensive group	41	Before treatment	1.45± 0.33	15.72± 3.21	5.35± 1.04
		After treatment	2.92± 0.39*#	8.28± 2.33*#	3.13± 0.52*#
Conventional group	41	Before treatment	1.43± 0.37	15.79± 3.32	5.32± 1.09
		After treatment	1.95± 0.38*	12.39± 2.57*	4.11± 0.62*

Note: Compared with before treatment, *$P<0.05$, compared with the conventional group after treatment, #$P<0.05$.

2.4 强化组与常规组治疗前后 TNF-α、IL-10、IL-18、MMP-9 水平变化对比

治疗前两组的 TNF-α、IL-10、IL-18、MMP-9 水平比较无统计学差异（$P>0.05$）；治疗后，强化组与常规组患者 TNF-α、IL-18、MMP-9 水平明显降低，IL-10 水平明显升高（$P<0.05$），且治疗后强化组患者的 TNF-α、IL-18、MMP-9 水平低于治疗后常规组，IL-10 高于常规组（$P<0.05$），见表 4。

表 4 强化组与常规组治疗前后 TNF-α、IL-10、IL-18、MMP-9 水平变化对比($\bar{x}\pm s$)

Table 4 The changes of TNF-, IL-10, IL-18 and MMP-9 levels between the intensive group and the routine group before and after treatment ($\bar{x}\pm s$)

Groups	n	Time	TNF-α(pg·L^{-1})	IL-10(ng·L^{-1})	IL-18(pg/mL)	MMP-9(μg/L)
Intensive group	41	Before treatment	110.09± 28.56	17.19± 4.21	117.68± 30.06	296.74± 63.33
		After treatment	76.18± 16.37*#	31.09± 6.86*#	71.42± 17.93*#	168.52± 42.18*#
Conventional group	41	Before treatment	109.12± 27.49	16．79± 4.42	119.33± 29.12	299.09± 61.94
		After treatment	91.19± 18.52*	22.06± 6.09*	97.58± 19.52*	234.18± 55.32*

Note: Compared with before treatment, *$P<0.05$, compared with the conventional group after treatment, #$P<0.05$.

3 讨论

近年来，较多研究证实 ACI 发病的重要原因为动脉粥样硬化，而炎症反应在动脉粥样硬化的发生中发挥着重要作用[11]。炎症反应包括抗炎因子与促炎因子，抗炎因子与促炎因子的比例失调是引发炎症反应的主要因素[12]。TNF-α 是一种促炎症因子，由 T 淋巴细胞核单核巨噬细胞分泌，在 ACI 患者炎性损伤中发挥着关键作用[13,14]。IL-10 是机体内一种重要的抗炎因子，对 TNF-α 等促炎性因子的产生具有抑制作用，ACI 患者发生脑缺血损伤时对脑部具有保护作用[15]。IL-18 是一种由单核巨噬细胞所分泌的促炎性因子，主要是通过释放 γ- 干扰素来促使炎症反应的发生，进而引发动脉粥样硬化[16]。MMP-9 可以使动脉粥样硬化斑块中的纤维蛋白原发生降解，使斑块的稳定性降低，进而导致斑块发生破裂，引发 ACI[17,18]。他汀类药物在治疗 ACI 中除了具备降脂作用外，还能够改善患者的血管内皮功能和降低炎性因子水平，使动脉斑块的稳定性得到提高[19]。在以往研究中显示，常规剂量的阿托伐他汀治疗 ACI 并不能取得理想的效果，近年来，较多学者开始应用强化剂量的阿托伐他汀对 ACI 患者进行强化治疗，并取得了较为理想的效果[20,21]。本研究结果显示，强化组与常规组患者的总有效率分别为 95.12%、80.49%，与常规组对比，强化组患者的临床总有效率明显升高，与以往研究结果相似[22]，提示阿托伐他汀强化降脂治疗 ACI 可显著提高治疗效果，同时相比常规组而言，强化组患者 TNF-α、IL-10、IL-18、MMP-9 水平的改善程度均较好，说明阿托伐他汀强化降脂治疗 ACI 能够更好的抑制炎性反应。

在治疗前后两组患者血脂水平变化分析中显示，强化组患

者治疗后 TC、TG、HDL-C、LDL-C 水平改善程度均优于常规组，说明强化剂量的阿托伐他汀的降脂效果更佳。除炎性因子与血脂在脑梗死中发挥重要作用外，纤溶系统活性也与 ACI 的发生有关，其中 t-PA 的减少或者 PAI-1 的升高，均会引发纤溶作用降低，进而引发产生血栓，FIB 水平的升高则会促使机体的血液粘稠度升高，也会增加动脉发生血栓的危险性，进而促使动脉粥样硬化的发生[23-25]。本研究结果显示，治疗后强化组患者的 t-PA 水平高于常规组，PAI-1、FIB 水平降低常规组，提示强化剂量的阿托伐他汀可显著增强纤溶活性，提高治疗效果。结合以上结果，强化剂量的阿托伐他汀治疗 ACI 的效果更好，且能够更好的改善患者相应的指标，分析其原因可能与阿托伐他汀存在量效效应有关，同时还可能与阿托伐他汀具有促进内皮型一氧化氮合酶合成有关，随着阿托伐他汀剂量的增加，一氧化氮合酶的水平升高，而一氧化氮合酶具有抗动脉粥样硬化及抗炎的效果，因此更有助于 ACI 患者的恢复[26,27]。

综上所述，阿托伐他汀强化降脂较常规剂量治疗 ACI 疗效显著提高，能够显著改善患者血脂、纤溶系统及炎症因子相关指标水平，具有降脂、调节纤溶活性及抑制炎症的作用。

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