doi: 10.13241/j.cnki.pmb.2017.05.004

辛伐他汀对大鼠蛛网膜下腔出血后脑血管痉挛的治疗效果研究 *

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摘要 目的：观察辛伐他汀对大鼠蛛网膜下腔出血后脑血管痉挛的治疗效果并探讨其可能机制。**方法：**将 48 只健康 Wistar 大鼠随机分为正常对照组、模型组、辛伐他汀组，每组各 16 只。模型组以及辛伐他汀组给予枕大池注入自体动脉血法以建立大鼠蛛网膜下腔出血后脑血管痉挛的动物模型，辛伐他汀组于第 1 次注血后开始给予辛伐他汀皮下注射，其余两组给予等体积生理盐水皮下注射。比较各组大鼠情况、组织学检查结果、蛛网膜下腔出血量评分、神经功能缺损评分、血管内径、血管舒张度、血管痉挛程度、eNOS 以及 TNF-α 蛋白表达水平。**结果：**实验过程中，正常对照组无大鼠死亡，模型组大鼠死亡率为 33.33%，辛伐他汀死亡率为 6.67%，较模型组显著降低(P<0.05)。治疗后，与正常对照组相比，模型组及辛伐他汀组大鼠蛛网膜下腔出血量评分及 TNF-α 阳性表达率较高(P<0.05)，神经功能缺损评分、血管内径、D/T 及 eNOS 阳性表达率较低(P<0.05)；与模型组相比，辛伐他汀组蛛网膜下腔出血量评分及 TNF-α 阳性表达率较低(P<0.05)，神经功能缺损评分、血管内径、D/T 及 eNOS 阳性表达率较高(P<0.05)。**结论：**辛伐他汀可有效改善蛛网膜下腔出血后脑血管痉挛，这可能与其上调 eNOS 蛋白表达并下调 TNF-α 蛋白表达有关。

关键词：辛伐他汀；蛛网膜下腔出血；脑血管痉挛；缺血性神经功能障碍

中图分类号：R743.35 **文献标识码：**A **文章编号：**1673-6273(2017)05-815-05

Efficacy of Simvastatin in the Treatment of Rats with Cerebral Vasospasm after Subarachnoid Hemorrhage*

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ABSTRACT Objective: To observe the efficacy of simvastatin on the treatment of cerebral vasospasm after subarachnoid hemorrhage in rats. **Methods:** 48 healthy WISTAR rats were divided into normal control group, model control group and simvastatin group, with 16 rats in each group. The rats in the model control group and model control group were given intracisternal injection of autologous arterial blood to establish the rat animal model of cerebral vasospasm after subarachnoid hemorrhage, and the rats in the simvastatin group were given simvastatin after the first injection of blood, while the other two groups were given saline subcutaneous injection. Then the rats situations, histological examination results, subarachnoid haemorrhage amount grade score, neural function defect score, blood vessel diameter, blood vessels tension degree, vasospasm degree, eNOS and TNF-α protein expression levels of the three groups were observed and compared. **Results:** In the experiment, there was no death in the normal control group, there were five rats died in the model control group with the death rate of 33.33%, and there was a rat died in the simvastatin group with the death rate of 6.67%. After treatment, compared with the normal control group, the subarachnoid haemorrhage amount score were higher in the model control group and simvastatin group (P<0.05), and neural function defect score, blood vessel diameter and D/T were lower (P<0.05); Compared with model control group, the subarachnoid haemorrhage amount score was lower in the simvastatin group (P<0.05), and neural function defect scale, blood vessel diameter and D/T were higher (P<0.05). Compared with normal control group, eNOS positive expression rate in the model control group and simvastatin group were lower (P<0.05), and the TNF-α positive expression rate was higher (P<0.05); Compared with model control group, the eNOS positive expression rate was higher in the simvastatin group (P<0.05), and the TNF-α positive expression rate was lower (P<0.05). **Conclusions:** Simvastatin in the treatment of subarachnoid hemorrhage is safe and effective, which can increase the eNOS protein expression, decrease the TNF-α protein expression, reduce the incidence rate of ischemic neurological dysfunction and blood vessel spasm, and it is expect to provide new methods of intervention for clinical treatment.

Key words: Simvastatin; Subarachnoid hemorrhage; Cerebral vasospasm; Ischemic nerve dysfunction

Chinese Library Classification(CLC): R743.35 Document code: A

Article ID: 1673-6273(2017)05-815-05

* 基金项目：陕西省自然科学基金项目(D201234)；西安市卫生和计划生育委员会科技项目(J201602035)
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(收稿日期：2016-09-06 接受日期：2016-09-28)

前言

脑血管痉挛(CVS)是指颈内动脉或者椎基底动脉系统出现动脉硬化斑块导致血管腔狭窄以及血流涡流,当血流涡流速度增加时,血管壁受刺激诱发致血管痉挛并出现短暂性脑缺血发作,当旋涡速度降低时上述症状消失。本病是蛛网膜下腔出血(SAH)所致的严重并发症,患病率极高,SAH 患者中超过 70%患有 CVS,其中有 17%~40%存在脑梗死等神经功能障碍,是临床致残、病死率较高的疾病之一[1-3]。辛伐他汀是他汀类的降血脂药物,能够有效控制和预防由于血液中胆固醇水平升高导致的心血管疾病[4]。研究表明阿托伐他汀能有效地控制 SAH 脑血管痉挛的发展[5],但是临床针对阿托伐他汀治疗蛛网膜下腔出血后脑血管痉挛的报道较少。因此,本研究采用蛛网膜下腔出血后脑血管痉挛模型大鼠,探讨辛伐他汀对蛛网膜下腔出血后脑血管痉挛模型大鼠蛛网膜下腔出血量评分、神经功能缺损评分、血管内径、血管舒张度、血管痉挛程度、eNOS 以及 TNF-α 蛋白表达水平影响。

1 材料与方法

1.1 材料

辛伐他汀 CAS 号:79902-63-9, 规格:100 mg/ 支, 货号:100601,青岛捷世康生物科技有限公司;戊巴比妥钠 CAS 号:57-33-0,规格:每支 5 g,货号:S013601,北京华迈科生物技术有限责任公司;10%甲醛溶液、苏木素以及伊红染料均由广州中医药大学实验动物中心提供。TNF-α 多克隆抗体(武汉伊莱瑞特生物科技有限公司),eNOS Polyclonal Antiserum eNOS 的多克隆抗体(上海宾智生物科技有限公司),专业图像分析软件 Image pro plus 6.0 /ipp 6.0 (柏奥易杰 (北京) 科技有限公司),HM525 冰冻切片机(西安金马医疗器械有限公司),近场光学显微镜 (德国 WItec Alpha300-SNOM),VENTANA VIAS 图像分析系统(上海巨纳科技有限公司)。

1.2 方法

1.2.1 实验分组 选择 48 只健康 Wistar 大鼠 SPF 级,雌雄各半,均为 8 周龄,体重(300± 30)g,大鼠购自北京维通利华实验动物技术有限公司(医动字第 19-055 号,动物许可证号:SYXK(京)2016-0121)。将 48 只大鼠随机分为正常对照组、模型对照组以及辛伐他汀组,每组各 16 只,分笼饲养,大鼠使用的笼具、饲料以及垫料等均高压消毒,能够正常自由饮食饮水,大鼠应用物品每隔 3 日进行消毒。适应性喂养 7 日,实验室温度维持于 23℃左右。

1.2.2 模型建立 所有大鼠用药前均接受 10 h 禁食水。正常对照组正常饲养,模型对照组以及辛伐他汀组给予枕大池注入自体动脉血法以建立大鼠蛛网膜下腔出血后脑血管痉挛的动物模型,于室温下,取仰卧位,头部低 30°,两组大鼠给予 1%戊巴比妥钠腹腔麻醉大鼠, 采用枕部正中切口并分离颈后肌群,暴露寰枕后膜,注射器缓慢吸入脑脊液约 0.1 mL,股动脉抽取自体动脉血 0.8 mL/kg,穿刺针经过寰枕后膜刺入枕大池,以 100 μ/min 缓慢进入血液,注射结束后,采用生物蛋白胶封闭针孔,头部低 30° 保持 30 min,血液均匀分布于脑池,正常对照组仅进行枕大池穿刺而不注血,给予各组大鼠正常颗粒食物以及充足自来水进行喂养,于 48 h 后再次重复注血。于造模结束后以及用药后每组各取 1 只大鼠麻醉后灌注处死,获取能够脑部标本,其中模型成功的标准为见到枕骨大池、极低池、小脑、大脑、脑干以及大脑表面有血块存在。

1.2.3 给药方法 辛伐他汀组于第 1 次注血后开始给予辛伐他汀(将辛伐他汀溶于碱性水解剂激活其化学活性)100 mg/100 g 皮下注射,每日一次,共用药 7 日,其余两组给予生理盐水皮下注射,剂量与使用频率和辛伐他汀组相同至实验结束。每日喂养全价饲料,自由饮水,保证充足饮水,维持每日人工排尿 3次。

1.2.4 指标观察 研究期间,观察并记录大鼠活动、饮食饮水以及毛色情况,测量体质量。所有受试大鼠均于用药第七日进行神经功能缺损评分, 参考 Garcia 标准对大鼠自发性活动、四肢运动对称、前脚伸展、攀登、对双侧躯干的接触反应以及触须反应进行评定,各项评分 1~3 分,其中计算总评分最低分 3 分,最高分 18 分为大鼠正常。在断头处死大鼠时将大鼠从左心室插入硅胶管进入升主动脉,丝线结扎,将 60 mL 注射器与硅胶管连接,动脉瘤夹夹闭胸主动脉,麻醉后迅速开颅取出含有基地动脉全长的脑干以及脑组织,进行病理观察,根据 Sugawara 的蛛网膜下腔出血量进行评分,根据出血量多少评分 1~3 分,0 分表示无出血;1 分为出血量极少;2 分为中等量的血凝块,能够分辨出血管;3 分为血凝块完全覆盖住全部脑血管, 对枕骨大池、极低池、小脑、大脑、脑干以及大脑表面六个部分的出血量进行评分,得出总出血量,分数区间为 0~18 分。采用 IPP 图像分析系统对大鼠基地动脉中断的动脉厚度以及内径进行检查,并通过口径的计算以判断血管痉挛程度,其中正常痉挛程度为 91%~100%; 轻度痉挛为 81%~90%; 中度痉挛为 70%~80%;重度痉挛为低于 70%。血管舒张度(D/T)即为动脉血管内径以及管壁厚度的比值, 其中正常痉挛程度为超过 85%;轻度痉挛为 61%~85%;中度痉挛为 40%~60%;重度痉挛为低于 40%。取大鼠脑组织进行石蜡包膜、HE 染色,并采用免疫组化法检测 eNOS 以及 TNF-α 在血管壁上的表达。按照视野内显示的染色程度进行评定,其中阴性为细胞浆内无染色或淡黄色染色;阳性为细胞中棕黄色颗粒状分布或棕黄色细腻颗粒弥漫分布。于光学显微镜下观察整张切片,寻找染色清晰、阳性细胞分布广的区域,并于每张切片中随机选择 5 个不同视野,以判断阳性细胞染色平均光密度(IOD)。

1.3 统计学方法

采用 SPSS 19.0 统计软件,计量资料以 $\bar{x}\pm s$ 表示,平均光密水平的表达采用 LSD-t 检验;计数资料采用%,组间比较方法为单因素方差法,采用 χ^2 检验。以 $P<0.05$ 视为差异有统计学意义。

2 结果

2.1 各组大鼠的一般情况

实验过程中严格遵守无菌操作,其中正常对照组无大鼠死亡,模型对照组大鼠 5 只死亡,死亡发生率为 33.33%;辛伐他汀组 1 只死亡,死亡发生率为 6.67%。正常对照组大鼠毛色光亮,活动正常,能够正常饮水饮食,四肢对称,大鼠能够提尾至桌子边缘,前腿伸展情况良好,四肢能够正常爬行,紧抓笼子有力,用钝木刺激大鼠能够迅速转头,双侧对称,钝木刺激大鼠一

侧胡须,双侧对称反应,平均体重为(310.72± 34.54)g;模型对照组大鼠毛色暗哑,活动度显著降低,进食困难,肢体行动极度无力甚至不能运动,大鼠提尾至桌子边缘,前腿仅有轻度伸展或基本无运动,四肢攀爬困难,无法紧抓笼子,用钝木刺激大鼠反应弛缓或仅有轻微反应,钝木刺激大鼠一侧胡须,双侧轻微反应或基本无反应,平均体重为(256.53± 27.20)g;辛伐他汀组造模期间大鼠毛色暗哑,但应用辛伐他汀皮下注射后,部分大鼠毛色恢复光亮,症状有所缓解,活动正常,饮食饮水正常,肢体行动移动较模型组好转,大鼠提尾至桌子边缘,前腿恢复伸展能力,四肢能够正常攀爬,可以紧抓笼子,用钝木刺激大鼠,反应较模型组迅速,钝木刺激大鼠一侧胡须,反应较模型组迅速,平均体重为(275.54± 31.36)g。

2.2 各组大鼠组织学检查结果

正常对照组大鼠的基底动脉组织结构基本正常,管腔未出现增厚,内膜光滑完整,平滑肌细胞未出现坏死;模型对照组大鼠的基底动脉组织结构出现不同程度的管腔狭窄, 管壁增厚,内膜存在褶皱,内皮细胞部分脱落,内弹力板褶皱,薄厚不一有断续,血管平滑肌细胞出现部分坏死;辛伐他汀组大鼠动脉血管痉挛较轻,管壁轻度增厚,内膜褶皱较为缓解,肌层以及外膜轻度增厚或者恢复正常。

2.3 各组大鼠蛛网膜下腔出血量评分以及神经功能缺损评分比较

治疗后,与正常对照组相比,模型组以及辛伐他汀组蛛网膜下腔出血量评分较高(P<0.05),神经功能缺损评分较低(P<0.05); 与模型组相比, 辛伐他汀组蛛网膜下腔出血量评分较低(P<0.05),神经功能缺损评分较高(P<0.05)。见表 1,图 1~3。

表 1 各组大鼠蛛网膜下腔出血量评分以及神经功能缺损评分比较($\bar{x}$± s)

Table 1 Comparison of the scores of subarachnoid hemorrhage and neurological deficits between different groups($\bar{x}$± s)

Groups	n	Subarachnoid hemorrhage score	Nerve function defect score
Normal control group	15	0	18.00
Model group	15	12.58± 1.57*	7.49± 0.83*
DMSim group	15	5.73± 0.62*#	13.15± 0.18*#

Note: Compared with the normal control group, *P<0.05. Compared with the model group, #P<0.05.

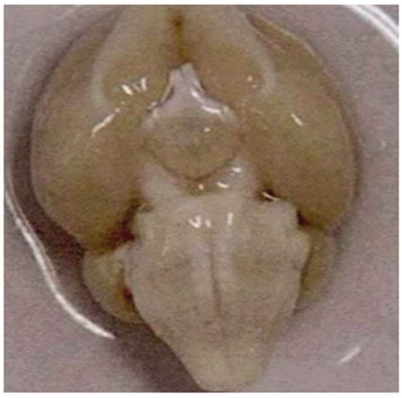

图 1 正常对照组蛛网膜下腔出血量代表性

Fig.1 The normal control group, the volume of subarachnoid hemorrhage in the representative;

图 2 模型对照组蛛网膜下腔出血量代表性

Fig.2 The model control group, the volume of subarachnoid hemorrhage

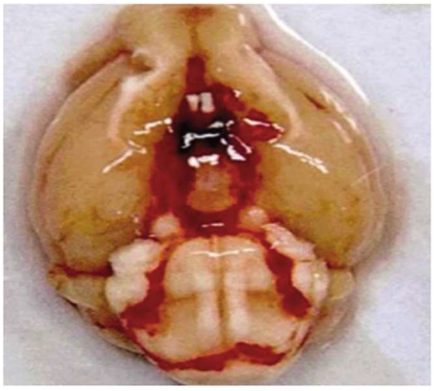

图 3 辛伐他汀组蛛网膜下腔出血量代表性图

Fig.3 The volume of the simvastatin group in subarachnoid hemorrhage

2.4 各组大鼠血管内径以及 D/T 水平比较

治疗后,与正常对照组相比,模型组以及辛伐他汀组血管内径以及 D/T 较低(P<0.05);与模型组相比,辛伐他汀组血管内径以及 D/T 较高(P<0.05)。见表 2-3,图 4~6。

表 2 各组大鼠血管内径以及 D/T 水平比较($\bar{x}$± s)

Table 2 Comparison of the blood vessel diameter and D/T level between different groups($\bar{x}$± s)

Groups	n	Blood vessel diameter(μm)	D/T
Normal control group	15	182.39± 20.39	14.39± 1.77
Model control group	15	128.39± 14.07*	8.30± 0.94*
DMSim group	15	163.93± 18.92*#	12.83± 1.68*#

Note: Compared with the normal control group, *P<0.05. Compared with the model group, #P<0.05.

2.5 各组大鼠 eNOS 以及 TNF-α 蛋白表达水平比较

治疗后,与正常对照组相比,模型组以及辛伐他汀组 eNOS 阳性表达率较低(P<0.05),TNF-α 阳性表达率较高(P<0.05);与模型组相比, 辛伐他汀组 eNOS 阳性表达率较高(P<0.05),TNF-α 阳性表达率较低(P<0.05)。见表 4,图 7~12。

3 讨论

蛛网膜下出血最常见的并发症为脑血管痉挛[6]。近年来,随

表 3 各组大鼠基底动脉痉挛程度的判定

Table 3 Determination of the degree of basilar artery spasm between different groups

Groups	Internal diameter				D/T			
	No spasm	Light	Moderate	Severe	No spasm	Light	Moderate	Severe
Normal control group	10	0	0	0	10	0	0	0
Model group	1	2	5	7	0	2	6	7
DMSim group	10	3	2	0	9	4	2	0

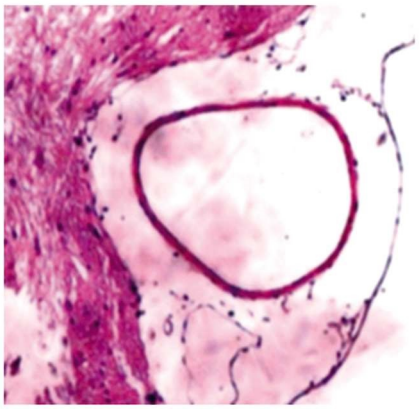

图 4 正常对照组基底动脉(HE,40×)

Fig.4 Basal artery of normal control group (HE, 40×)

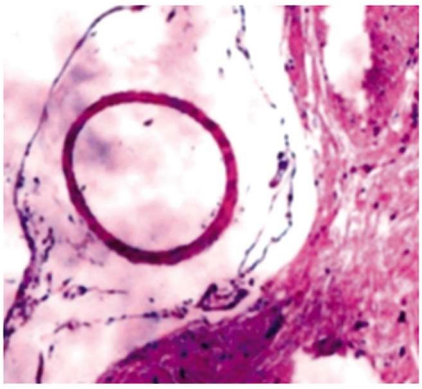

图 5 模型对照组基底动脉(HE,40×)

Fig.5 Model control group basal artery (HE, 40×)

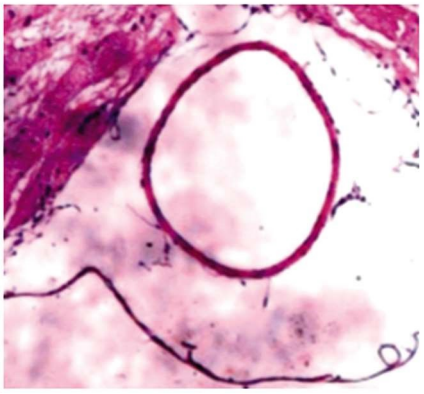

图 6 辛伐他汀组基底动脉(HE,40×)

Fig.6 Simvastatin group of basilar artery (HE, 40×)

表 4 各组大鼠 eNOS 以及 TNF-α 的表达比较(IOD 值,$\bar{x}\pm$ s)

Table 4 Comparison of the eNOS and TNF- expression between different groups(IOD, $\bar{x}\pm$ s)

Groups	n	eNOS	TNF-α
Normal control group	15	0.365± 0.045	0.214± 0.030
Model group	15	0.275± 0.032*	0.410± 0.052*
DMSim group	15	0.332± 0.039*#	0.302± 0.036*#

Note: Compared with the normal control group, *P<0.05. Compared with the model control group, #P<0.05.

图 7 正常对照组基底动脉 eNOS 的表达情况

Fig.7 Expression of eNOS in the basal artery of the normal control group

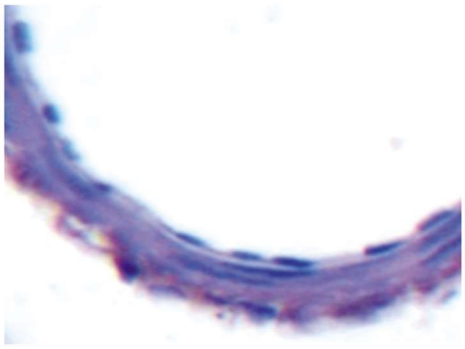

图 8 模型对照组基底动脉 eNOS 的表达情况

Fig.8 Expression of eNOS in basal artery of model control group

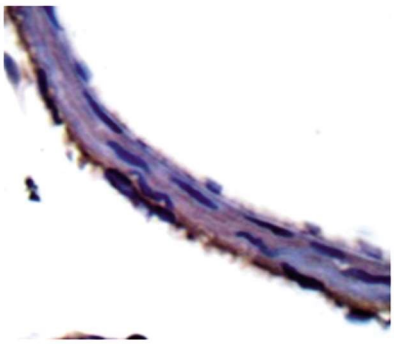

图 9 辛伐他汀组基底动脉 eNOS 的表达情况

Fig.9 Expression of eNOS in simvastatin group

着诊疗手段的不断进步,血管瘤再出血所致的死亡发生率明显降低,目前唯一有效的治疗药物是尼莫地平,能够改善蛛网膜下出血预后,但无法预防血管痉挛[7]。辛伐他汀是土曲霉发酵产物的合成衍生物,能够通过抑制内源性胆固醇合成,从而预防和缓解高血压以及冠心病的发生发展[8]。近年来,辛伐他汀不仅应用于降血脂,还能够抗炎、抗氧化、调节免疫功能、抑制血管平滑肌细胞的增值以及改善内皮细胞功能[9]。本研究结果显示:实验过程中蛛网膜下腔出血后脑血管痉挛大鼠 5 只死亡,死亡发生率为 33.33%; 而辛伐他汀组 1 只死亡, 死亡发生率为 6.67%, 表明辛伐他汀能够降低蛛网膜下腔出血后脑血管痉挛大鼠的死亡率。

蛛网膜下腔出血后脑血管痉挛的基本特点为血管壁增厚,

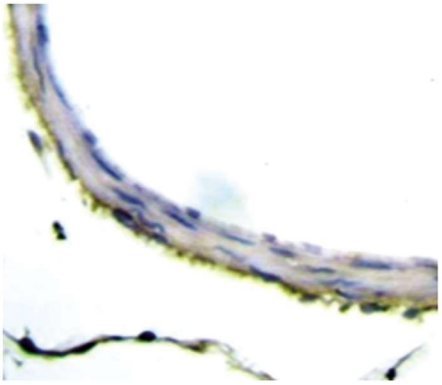

图 10 正常对照组基底动脉 TNF-α 的表达情况

Fig.10 The expression of TNF-α in the basal artery of the normal control group

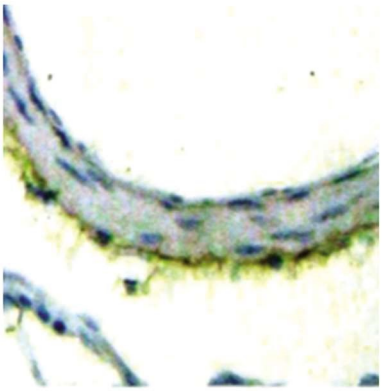

图 11 模型对照组基底动脉 TNF-α 的表达情况

Fig.11 The expression of TNF-α in basal artery of model control group

图 12 辛伐他汀组基底动脉 TNF-α 的表达情况

Fig.12 The expression of TNF- αin simvastatin group

血管内径缩小[10]。研究显示[11,12]典型血管痉挛内经不完全较无血管痉挛的基底动脉内经小,由于同级别供血动脉管腔内经和管壁厚度之比基本稳定,因此血管舒张度(D/T)是最能够全面反映血管痉挛情况的指标。本研究结果显示:与正常对照组相比,蛛网膜下腔出血后脑血管痉挛模型组以及辛伐他汀组大鼠治疗后蛛网膜下腔出血量评分较高,神经功能缺损评分、血管内径以及 D/T 较低;与蛛网膜下腔出血后脑血管痉挛组相比,辛伐他汀组蛛网膜下腔出血量评分较低,神经功能缺损评分、血管内径以及 D/T 较高,提示辛伐他汀能够减轻蛛网膜下腔出血后脑血管痉挛。

CVS 分为早发性以及迟发性,多发生于 SAH 后 0.5 h~7 d 内,患者多存在血管舒张以及收缩的失调[13],但发病机制尚未明确。血管内皮功能失调导致一氧化氮(NO)介导的内皮依赖性血管舒张反应降低,合成 NO 的关键酶是一氧化氮酶(NOS),NOS 分为不同亚型,主要存在于内皮细胞以及神经细胞内的是内皮型一氧化氮酶(eNOS)[14]。血管内皮产生的 NO 和内源性收缩因子能够调节舒张肌,内皮受损或产生的舒张因子受损均可使其失衡,诱发血管痉挛[15]。有研究显示[16]蛛网膜下腔出血后脑血管痉挛存在血管内皮组织和内皮依赖性舒张反应损伤,NO 水平降低。此外,SHA 大鼠体外实验显示 NO 的替代治疗能够逆转 CVS。国外学者制作猴子 SAH 模型,发现痉挛的大脑内 eNOSmRNA 的蛋白表达水平降低[17]。TNF-α 参与多种炎症反应和免疫应答的细胞因子,不仅能够诱导内皮细胞以及白细胞产生黏附分子,还可以促进白细胞对毛细血管内皮的黏附功能,同时促发损伤级联反应[18]。曾有研究证实[19,20]急性脑血管疾病中 TNF-α 水平持续升高并造成脑血管进一步受损,其水平改变与基底动脉血流量变化在时间以及程度上具有一致性,预后不良患者 TNF-α 水平则显著增高。

综上所述,辛伐他汀可有效改善蛛网膜下腔出血后脑血管痉挛,这可能与其上调 eNOS 蛋白表达并下调 TNF-α 蛋白表达有关。

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