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# 阿托伐他汀联合尼莫地平治疗蛛网膜下腔出血的临床疗效及对血清 S-100B、Ang 水平的影响 *

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**摘要 目的:**探讨阿托伐他汀联合尼莫地平治疗蛛网膜下腔出血的临床疗效及对患者血清蛋白(S-100B)、血管生成素(Ang)水平的影响。**方法:**选择 2015 年 1 月至 2016 年 1 月我院收治的蛛网膜下腔出血患者 90 例,采用随机数表法分为观察组(n=45)和对照组(n=45)。观察组采用阿托伐他汀联合尼莫地平进行治疗,对照组采用尼莫地平治疗。比较两组患者的临床疗效及治疗前后脑动脉平均血流速度、美国国立卫生研究院卒中量表(NIHSS)、日常生活能力量表(BI)、血清 S-100B、人血管生成素(ANG)水平的变化及不良反应的发生情况。**结果:**治疗后,观察组总有效率为 93.33%,显著高于对照组(73.33%,*P<0.05*)。治疗后,两组患者脑动脉平均血流速度、NIHSS 及 BI 评分均较治疗前明显改善,且观察组患者脑动脉平均血流速度、BI 评分均高于对照组;NIHSS 评分明显低于对照组(*P<0.05*);治疗后,两组血清 S-100B、ANG 水平较治疗前均显著降低(*P<0.05*),且观察组血清 S-100B、ANG 水平均明显低于对照组(*P<0.05*)。观察组并发症发生率为 13.33%,明显低于对照组(46.67%,*P<0.05*)。**结论:**阿托伐他汀联合尼莫地平治疗蛛网膜下腔出血患者的疗效及安全性均明显优于单用尼莫地平治疗治疗,可能与其有效降低血清 S-100B、ANG 水平有关。

**关键词:**阿托伐他汀;尼莫地平;蛛网膜下腔出血;S-100B;人血管生成素

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# Curative Efficacy of Atorvastatin Combined with Nimodipinein in the Treatment of Subarachnoid Hemorrhage and Its Effects on the Serum s-100b and Ang Levels*

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**ABSTRACT Objective:** To study the efficacy of Atorvastatin combined with nimodipine in the treatment of Subarachnoid hemorrhage and its effects on the serum Protein (s-100b), angiopoietin (Ang) levels. **Methods:** 90 patients with subarachnoid hemorrhage admitted to our hospital from January 2015 to January 2016 were selected and divided into the observation group (n=45) and the control group (n=45) by the random number table method. The observation group was treated with atorvastatin combined with nimodipine, while the control group was treated with nimodipine. The clinical efficacy, changes of mean cerebral artery blood flow velocity, national institutes of health stroke scale (NIHSS), daily living ability scale (BI), serum s-100, and human angiopoietin (ANG) levels and the incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was 93.33%, which was significantly higher than that of the control group (73.33%, *P<0.05*). After treatment, the mean cerebral artery blood flow velocity, NIHSS and BI scores of patients in both groups were significantly improved compared with those before treatment, and the mean cerebral artery blood flow velocity and BI scores of patients in the observation group were higher than those in the control group. The NIHSS score was significantly lower than that of the control group (*P<0.05*). After treatment, the serum s-100 and ANG levels in both groups were significantly lower than those before treatment (*P<0.05*), and serum s-100 and ANG levels in the observation group were significantly lower than those in the control group (*P<0.05*). The incidence of complications in the observation group was 13.33%, which was significantly lower than that in the control group (46.67%, *P<0.05*). **Conclusion:** The efficacy and safety of atorvastatin combined with nimodipine in the treatment of patients with subarachnoid hemorrhage are significantly better than that of nimodipine alone, which may be related to its effective reduction of serum s-100 and ANG levels.

**Key words:** Atorvastatin; Nimodipine; Subarachnoid hemorrhage; S-100B; Human angiopoietin

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## 前言

蛛网膜下腔出血(subarachnoid hemorrhage,SAH)是指颅底或脑表面的病灶破裂,导致血液直接流向蛛网膜下腔引致的临床综合征,又被称为原发性蛛网膜下腔出血,占急性脑卒中的10%,是颅脑创伤后继发脑积水、脑血管痉挛、脑梗死的主要因素[1,2]。有研究报道,早期应用血管扩张剂能有效提高蛛网膜下腔出血患者的疗效[3,4]。目前,临床上大多数使用尼莫地平治疗此病,但单一运用此药的疗效并不理想,部分患者会出现脑血管痉挛、复发出血等不良并发症[5,6]。

有研究显示患者发生脑痉挛与炎症和血管内皮功能障碍有关,而他汀类药物具有抗炎和改善血管内皮功能[7,8]。阿托伐他汀是一种具有保护神经和改善蛛网膜下腔出血后脑血管痉挛的化学物质,治疗蛛网膜下腔出血具有良好的有效性和安全性[9]。有研究显示,S-100B 能够反映胶质细胞破坏,间接反映神经元的损伤[10]。S-100β 蛋白是近年发展起来的血清标记物,是由星形胶质细胞和少突胶质细胞合成的,是神经系统中急性期细胞损伤的指标;Ang 是一族分泌型的生长因子,具有分泌型信号肽的典型特征。本研究主要探讨了阿托伐他汀联合尼莫地平治疗蛛网膜下腔出血的临床疗效及对患者血清 S-100B、Ang 水平的影响,结果报道如下。

## 1 资料与方法

### 1.1 一般资料

选取 2015 年 1 月至 2016 年 1 月我院收治的 90 例 SAH 患者进行研究,研究已获得我院伦理会批准实施。纳入标准[11]:(1)首次发病,且伴有头痛。呕吐症状;(2)血管造影及头颅检查确诊;(3)非血肿、脑实质出血患者。排除标准:(1)患有严重心、肝、肾疾病者;(2)需要开颅手术患者(3)对本次药物过敏者。将入选患者随机分为两组,观察组男 25 例,女 20 例,年龄 44~61 岁,平均(54.78± 2.35)岁;对照组男 23 例,女 22 例,年龄 46~62 岁。平均(55.21± 2.15)岁。两组患者性别($x^2$=0.179,$P$=0.673)、年龄(t=0.906,$P$=0.368)等一般资料比较差异均无统计学意义($P>0.05$),具有可比性。

### 1.2 方法

对照组采用尼莫地平治疗,患者口服尼莫地平 (规格 20 mg,厂家:四川科伦药业股份有限公司,国药准字 H10983188),30~50 mg/ 次,一天三次。观察组采用阿托伐他汀联合尼莫地平治疗,在对照组的基础上服用阿托伐他汀(规格 20 mg,厂家:Pfizer Ireland Pharmaceuticals,国药准字 J20120049)20 mg,一天一次。两组均治疗 30d,评价疗效和记录不良反应。

### 1.3 观察指标

疗效判断标准[12]:(1)基本痊愈:临床症状基本消失,日常生活不受影响;(2)好转:临床症状有明显改善,生活部分可以自理,遗留不同程度后遗症;(3)无效:生活不能自理,症状无明显改善,患者生活不能自理。基本痊愈+好转为有效率。血清S-100 B 及 Ang 水平均采用 ELISA 法测定,严格按照说明书操作。

NIHSS 评分量表:正常:0~1 分;轻度卒中:1~4;中度卒中:5~15 分;中 ~ 重度卒中:15~20 分;重度卒中:21~42 分。

BI 评分量表:100 分代表生活自理;61~99 分代表轻度功能障碍;41~60 分代表中度功能障碍;≤ 40 分代表重度功能障碍。

### 1.4 统计学分析

以 SPSS18.0 软件包处理,计量资料均为正态分布,用均数± 标准差($\bar{x}\pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示,组间比较采用 $x^2$ 检验,以 $P<0.05$ 表示差异具有统计学意义。

## 2 结果

### 2.1 两组患者临床疗效的比较

治疗后,两组患者总有效率分别为 93.33%、73.33%,观察组显著高于对照组($P<0.05$),详见表 1。

表 1 两组患者疗效对比[例(%)]

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

| Groups | n | Effective | Valid | Invalid | Total effective rate |
|---|---|---|---|---|---|
| Observation group | 45 | 26(57.78) | 16(35.56) | 3(6.67) | 42(93.33) |
| The control group | 45 | 19(42.22) | 14(31.11) | 12(26.67) | 33(73.33) |
| $x^2$ value | | | | | $x^2$=6.480 |
| $P$ value | | | | | 0.011 |

### 2.2 两组患者治疗前后脑动脉平均血流速度、NIHSS 及 BI 比较

两组患者治疗前脑动脉平均血流速度、NIHSS 及 BI 评分比较差异无明显统计学意义($P>0.05$);治疗后,两组患者脑动脉平均血流速度、NIHSS 及 BI 评分均较治疗前明显改善,且观察组脑动脉平均血流速度、BI 评分均显著高于对照组,NIHSS 评分明显低于对照组($P<0.05$),详见表 2。

### 2.3 两组患者治疗前后血清 S-100B、ANG 水平比较

治疗后,两组血清 S-100B、ANG 水平均较治疗前显著降低($P<0.05$),且观察组血清 S-100、ANG 水平明显低于对照组($P<0.05$),见表 3。

## 3 讨论

蛛网膜下腔出血是常见的一种急症病症,是导致颅内动脉瘤破裂的因素,主要是由于动脉壁因局部病变而向外膨出,形成的永久性扩张[13,14]。患者临床表现为头痛、恶心、呕吐等症状,多发于 30~60 岁的青壮年[15],其主要致死原因是脑血管痉挛。有研究显示脑血管痉挛的发生率高达 50%以上[16,17]。因此,控制脑血管痉挛是治疗的关键。目前临床上大多数使用尼莫地平治

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表 2 两组患者治疗前后脑动脉平均血流速度、NIHSS 及 BI 的比较($\bar{x}\pm s$)

Table 2 Comparison of the mean cerebral artery blood flow velocity, NIHSS and BI between the two groups before and after treatment($\bar{x}\pm s$)

| Groups | n | Mean blood flow velocity(cm/s) | | NIHSS | | BI | |
|---|---|---|---|---|---|---|---|
| | | Before the treatment | After treatment | Before the treatment | After treatment | Before the treatment | After treatment |
| Observation group | 45 | 81.84± 12.51 | 116.75± 13.25 | 22.65± 3.12 | 9.36± 2.41 | 20.82± 2.95 | 73.27± 10.15 |
| The control group | 45 | 79.46± 11.28 | 103.41± 12.98 | 22.18± 3.35 | 15.23± 3.58 | 21.24± 3.18 | 51.21± 7.29 |
| t value | | 0.948 | 4.825 | 0.689 | 9.124 | 0.650 | 11.842 |
| *P* value | | 0.346 | 0.000 | 0.493 | 0.000 | 0.518 | 0.000 |

表 3 两组患者治疗前后血清 S-100B、ANG 水平的比较[$\bar{x}\pm s$,(μg/L)]

Table 3 Comparison of the serum s-100 and ANG levels between the two groups before and after treatment[$\bar{x}\pm s$,(μg/L)]

| Groups | n | S-100 B | | ANG-1 | | ANG-2 | |
|---|---|---|---|---|---|---|---|
| | | Before the treatment | After treatment | Before the treatment | After treatment | Before the treatment | After treatment |
| Observation group | 45 | 1.21± 0.21 | 0.52± 0.18 | 70.32± 12.26 | 40.51± 8.84 | 5.95± 0.82 | 2.56± 0.36 |
| The control group | 45 | 1.18± 0.31 | 0.81± 0.27 | 69.89± 11.38 | 54.14± 8.53 | 5.93± 0.91 | 3.79± 0.45 |
| *t* value | | 0.538 | 5.995 | 0.172 | 7.443 | 0.110 | 14.318 |
| *P* value | | 0.592 | 0.000 | 0.864 | 0.000 | 0.913 | 0.000 |

疗此病,尼莫地平是一种脂溶性较强的药物,是第二代双氢益生物类钙离子拮抗剂,广泛应用于临床治疗血管痉挛,主要通过阻断动脉血管平滑肌细胞电压门控钙通道,减少细胞外钙转移到细胞内,起到扩张微血管小动脉、脑循环阻力,从而减少脑水肿的发生[18,19]。在临床上使用尼莫地平治疗蛛网膜下腔出血十分常见,且有一定的疗效,但在此过程中,为了防止部分患者对尼莫地平的反应过强,从而发生低血压、脑供血等情况,应严格监测患者血压,根据血压进行调整药物的剂量[20,21]。

有研究显示他汀类药物对心脑血管疾病具有有较好的疗效[22]。阿托伐他汀又叫立普妥,是一种化学品,可诱导血管壁平滑肌细胞凋亡,管腔狭窄是因为平滑肌细胞的凋亡不足时内膜损伤所导致的,且其还具有改善脑血流量、抗炎、增加一氧化氢合酶活性等作用[23,24]。本研究结果显示联合用药的临床总有效率明显高于单药治疗的患者,分析是因为阿托伐他汀增加了内皮细胞合成酶的含量,阻止了血管内皮细胞的凋亡和增殖,提高了临床疗效。Carpenter C R[25]等研究报道阿托伐他汀具有抗炎症和改善血管内皮功能等作用。本研究结果还显示使用阿托伐他汀联合尼莫地平治疗的患者的平均血流速度、NIHSS、BI 改善情况明显好于单纯使用尼莫地平治疗的患者,提示阿托伐他汀联合尼莫地平可有效改善患者的平均血流速度、NIHSS、BI,提高生活质量,分析是因为阿托伐他汀是一种降血脂和降胆固醇药物,具有诱导血管平滑肌细胞凋亡的作用,从而改善患者血管内膜细胞的增殖增多,进而防止脑血管的狭窄,改善了患者的脑动脉的各项指标。

S-100B 是星形胶质细胞激活的标志之一,是一组低分子量的钙结合蛋白,对中枢神经系统的胶质细胞具有高度特异性,在细胞增生、分化、凋亡中具有重要意义[27,28],有研究显示是脑损伤的生化标志物[26]。ANG 是一组分泌型生长因子,由 ANG-1—ANG-4 组成,能够具有分泌型信号肽的典型特征,能够增加血脑屏障内皮细胞间连接的紧密度,从而降低血管的通透性,减少神经功能损害[29,30]。本研究结果显示使用阿托伐他汀联合尼莫地平治疗的患者的血清 S-100B、Ang 明显改善,且低于单纯使用尼莫地平治疗的患者,提示阿托伐他汀联合尼莫地平可有效的降低患者的血清 S-100B、Ang 水平。分析原因是可能因为阿托伐他汀在蛛网膜下腔出血中可以减少炎性因子的表达,降低血管周围的炎症反应,减少周围组织损伤,维持正常的血管功能的作用,最终降低其 S-100B、Ang 水平。此外,阿托伐他汀联合尼莫地平治疗的并发症发生率明显低于单纯使用尼莫地平的患者,提示联合用药优于单纯使用尼莫地平治疗,且安全性更高。

综上所述,阿托伐他汀联合尼莫地平治疗蛛网膜下腔出血患者的疗效及安全性均明显优于单用尼莫地平治疗治疗,可能与其有效降低血清 S-100B、ANG 水平有关。

## 参 考 文 献(References)


[1] Naidech A, Du Y, Kreiter K T, et al. Dobutamine versus milrinone after subarachnoid hemorrhage[J]. Neurosurgery, 2016, 56(1): 26-27

[2] Mahmoud SH, Buxton J. Seizures and Choice of Antiepileptic Drugs Following Subarachnoid Hemorrhage: A Review [J]. Can J Neurol Sci, 2017, 44(6): 643-653

[3] Boukobza M, Crassard I, Bousser M G, et al. Radiological findings in cerebral venous thrombosis presenting as subarachnoid hemorrhage: a series of 22 cases[J]. Neuroradiology, 2016, 58(1): 11-16

[4] Shao A, Wu H, Yuan H, et al. Hydrogen-Rich Saline Attenuated Subarachnoid Hemorrhage-Induced Early Brain Injury in Rats by Suppressing Inflammatory Response: Possible Involvement of NF-κB Pathway and NLRP3 Inflammasome [J]. Molecular Neurobiology, 2016, 53(5): 3462-3476

[5] Ng YH, Pilcher DV, Bailey M et al. Predicting medical emergency team calls, cardiac arrest calls and re-admission after intensive care discharge: creation of a tool to identify at-risk patients [J]. Anaesth Intensive Care, 2018, 46(1): 88-96


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[6] Fujimoto M, Shiba M, Kawakita F, et al. Deficiency of tenascin-C and attenuation of blood-brain barrier disruption following experimental subarachnoid hemorrhage in mice [J]. Journal of Neurosurgery, 2016, 124(6): 1693-1702

[7] Rumalla K, Reddy A Y, Mittal M K. Association of Recreational Marijuana Use with Aneurysmal Subarachnoid Hemorrhage [J]. Journal of Stroke & Cerebrovascular Diseases, 2016, 25(2): 452-460

[8] Dong Y, Fan C, Hu W, et al. Melatonin attenuated early brain injury induced by subarachnoid hemorrhage via regulating NLRP3 inflammasome and apoptosis signaling[J]. Journal of Pineal Research, 2016, 60(3): 253-262

[9] Sayer D, Bloom B, Fernando K, et al. An Observational Study of 2,248 Patients Presenting With Headache, Suggestive of Subarachnoid Hemorrhage, Who Received Lumbar Punctures Following Normal Computed Tomography of the Head [J]. Academic E mergency Medicine, 2016, 22(11): 1267-1273

[10] Pearson TE, Frizzola MA, Priest MA, et al. Pediatric Extracorporeal Cardiopulmonary Resuscitation Patient With Traumatic Subarachnoid Hemorrhage and Takotsubo Syndrome[J]. Air Med J, 2018, 37(1): 64-66

[11] Nishikawa H, Suzuki H. Implications of periostin in the development of subarachnoid hemorrhage-induced brain injuries [J]. Neural Regen Res, 2017, 12(12): 1982-1984

[12] Rumalla K, Reddy A Y, Mittal M K. Association of Recreational Marijuana Use with Aneurysmal Subarachnoid Hemorrhage [J]. Journal of Stroke & Cerebrovascular Diseases, 2016, 25(2): 452-460

[13] Turan N, Heider R A, Zaharieva D, et al. Sex Differences in the Formation of Intracranial Aneurysms and Incidence and Outcome of Subarachnoid Hemorrhage: Review of Experimental and Human Studies[J]. Translational Stroke Research, 2016, 7(1): 12-19

[14] Frontera J A, Provencio J J, Sehba F A, et al. The Role of Platelet Activation and Inflammation in Early Brain Injury Following Subarachnoid Hemorrhage[J]. Neurocritical Care, 2016, 26(1): 1-10

[15] Diringer MN, Zazulia AR. Aneurysmal Subarachnoid Hemorrhage: Strategies for Preventing Vasospasm in the Intensive Care Unit [J]. Semin Respir Crit Care Med, 2017, 38(6): 760-767

[16] Suwatcharangkoon S, Meyers E, Falo C, et al. Loss of Consciousness at Onset of Subarachnoid Hemorrhage as an Important Marker of Early Brain Injury[J]. Jama Neurol, 2016, 73(1): 28-35

[17] Gard A P, Sayles B D, Robbins J W, et al. Hemorrhage Rate After External Ventricular Drain Placement in Subarachnoid Hemorrhage: Time to Heparin Administration [J]. Neurocritical Care, 2017, 27(3): 1-6

[18] Siegler J E, Marcaccio C, Nawalinski K, et al. Elevated Red Cell Distribution Width is Associated with Cerebral Infarction in Aneurysmal Subarachnoid Hemorrhage [J]. Neurocritical Care, 2016, 26(1): 1-8

[19] Jabbarli R, Reinhard M, Roelz R, et al. The predictors and clinical impact of intraventricular hemorrhage in patients with aneurysmal subarachnoid hemorrhage [J]. International Journal of Stroke, 2016, 11(1): 68-76

[20] van Donkelaar C E, Bakker N A, Veeger N J, et al. Prediction of outcome after subarachnoid hemorrhage: timing of clinical assessment[J]. Journal of Neurosurgery, 2016, 126(1): 1-8

[21] Nanba T, Kashimura H, Saura H, et al. Subarachnoid hemorrhage due to ruptured intracranial aneurysm following posterior reversible encephalopathy syndrome [J]. Journal of Neurosciences in Rural Practice, 2016, 7(3): 440-442

[22] van Dijk B J, Vergouwen M D, Kelfkens M M, et al. Glial cell response after aneurysmal subarachnoid hemorrhage-functional consequences and clinical implications[J]. Biochimica Et Biophysica Acta, 2016, 1862(3): 492-505

[23] Obata Y, Takeda J, Sato Y, et al. A multicenter prospective cohort study of volume management after subarachnoid hemorrhage: circulatory characteristics of pulmonary edema after subarachnoid hemorrhage[J]. Journal of Neurosurgery, 2016, 125(2): 254-263

[24] Washington C W, Derdeyn C P, Dhar R, et al. A Phase I proof-of-concept and safety trial of sildenafil to treat cerebral vasospasm following subarachnoid hemorrhage [J]. Journal of Neurosurgery, 2016, 124(2): 318-327

[25] Carpenter C R, Hussain A M, Ward M J, et al. Spontaneous Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis Describing the Diagnostic Accuracy of History, Physical Exam, Imaging, and Lumbar Puncture with an Exploration of Test Thresholds[J]. Academic Emergency Medicine Official Journal of the Society for Academic Emergency Medicine, 2016, 23(9): 963-1003

[26] Kunze E, Stetter C, Willner N, et al. Effects of Fluid Treatment With Hydroxyethyl Starch on Renal Function in Patients With Aneurysmal Subarachnoid Hemorrhage [J]. J Neurosurg Anesthesiol, 2016, 28(3): 187-194

[27] Adams H, Ban V S, Leinonen V, et al. Risk of Shunting After Aneurysmal Subarachnoid Hemorrhage: A Collaborative Study and Initiation of a Consortium[J]. Stroke, 2016, 47(10): 2488-2496

[28] Sandow N, Diesing D, Sarrafzadeh A, et al. Nimodipine Dose Reductions in the Treatment of Patients with Aneurysmal Subarachnoid Hemorrhage[J]. Neurocritical Care, 2016, 25(1): 29-39

[29] Garland P, Durnford A J, Okemefuna A I, et al. Heme Hemopexin Scavenging Is Active in the Brain and Associates With Outcome After Subarachnoid Hemorrhage[J]. Stroke, 2016, 47(3): 872-876

[30] Varvarousi G, Xanthos T, Sarafidou P, et al. Role of levosimendan in the management of subarachnoid hemorrhage[J]. American Journal of Emergency Medicine, 2016, 34(2): 298-306

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