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阿托伐他汀对慢性硬膜下血肿患者术后 MBI、CSS 评分的影响 *

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摘要 目的:探讨阿托伐他汀对慢性硬膜下血肿(CSDH)术后改良 Barthel 指数(MBI)和中国卒中量表(CSS)评分的影响。**方法:**选择 2014 年 2 月至 2019 年 2 月我院接诊的 126 例 CSDH 术后患者进行研究,通过随机数表法将其分为观察组和对照组,每组各 63 例。两组患者均接受钻孔引流术,对照组术后给予常规处理,观察组联合阿托伐他汀口服治疗,均持续用药 1 个月。比较两组治疗前后血清神经元特异性烯醇化酶(NSE)、人 S100B 蛋白(S-100B)、肿瘤坏死因子-α(TNF-α)、白介素-1(IL-1)、MBI、CSS 评分的变化情况及不良反应的发生情况和复发情况。**结果:**观察组治疗后血清 NSE、S-100B、CRP、TNF-α、IL-1 水平均低于对照组 ($P < 0.05$), MBI 评分高于对照组, CSS 评分低于对照组($P < 0.05$);两组不良反应发生率比较差异无统计学意义($P > 0.05$), 观察组复发率明显低于对照组($P < 0.05$)。**结论:**阿托伐他汀能降低 CSDH 患者术后炎症反应,提高 MBI、CSS 评分,降低复发率,且不增加不良反应。

关键词:慢性硬膜下血肿;阿托伐他汀;炎症;改良 Barthel 指数;中国卒中量表**中图分类号:**R651.15 文献标识码:A 文章编号:1673-6273(2020)18-3582-05

Effect of Atorvastatin on the MBI and CSS Scores of Chronic Subdural Hematoma Patients after Operation*

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ABSTRACT Objective: To explore the effect of atorvastatin on the modified Barthel index (MBI) and Chinese stroke scale (CSS) scores in patients with chronic subdural hematoma (CSDH). **Methods:** A total of 126 postoperative patients with CSDH treated in our hospital from February 2014 to February 2019 were selected for study. They were divided into observation group and control group by random number table method, with 63 cases in each group. The patients in both groups were treated by drilling and drainage. The patients in the control group were treated with routine treatment after operation. The observation group was treated with atorvastatin orally for one month. Before and after treatment, the serum neuron-specific enolase (NSE), human S100B protein (S-100B), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), MBI, CSS scores were compared. Changes and the occurrence and recurrence of adverse reactions. **Results:** After treatment, the levels of serum NSE, S-100B, CRP, TNF-α and IL-1 as well as CSS score in the observation group were lower than those in the control group ($P < 0.05$), while the MBI score was higher than the control group ($P < 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). The recurrence rate in the observation group was significantly lower than that in the control group ($P < 0.05$). **Conclusion:** Atorvastatin can relieve the postoperative inflammatory reaction, improve MBI and CSS scores, reduce the recurrence rate without increasing the adverse reactions.

Key words: Chronic subdural hematoma; Atorvastatin; Inflammation; Coagulation function; Modified Barthel index; Chinese Stroke Scale

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前言

慢性硬膜下血肿(CSDH)发生率约占颅内血肿的 10%, 随着人口老龄化, 抗凝剂、抗血小板药物使用的增加, 其发病率逐

年升高^[1,2]。CSDH 的发病机制尚不完全清楚, 研究表明主要与以下原因有关:(1)头部外伤导致桥静脉撕裂, 形成血肿, 引起炎症反应, 形成特征性的易渗漏的血管“新膜”, 从这些血管中渗漏的血液导致血肿扩大^[3,4];(2)轻度创伤或者颅骨不对称造成

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的硬脑膜与蛛网膜之间的张力增加，最终导致脑脊液泄露，形成硬膜下积液。之后积液引起炎症反应，导致“新膜”形成，其外膜的脆性血管反复出血形成^[5,6]。目前，用于CSDH术后的药物血管紧张素转化酶抑制剂、甘露醇、头孢曲松钠，以上的药物均有一定的临床副作用，不利于患者预后的恢复^[7,8]。阿托伐他汀近年来常用于高血脂和冠心病的临床治疗，且研究显示其能降低血肿内炎症因子的表达，促进血肿膜血管生成^[9,10]，但对术后MBI、CSS评分的影响及机制不完全明确。因此，本文主要探讨了阿托伐他汀对慢性硬膜下血肿(CSDH)术后炎症因子及MBI、CSS评分的影响。

1 资料与方法

1.1 一般资料

选择我院2014年2月至2019年2月接诊的126例CSDH术后的患者，纳入标准：①符合慢性硬膜下血肿诊疗规范及指南，并经颅脑CT或MRI检查确诊^[11,12]；②临床表现以颅内压升高、头痛加剧为主，并伴有面部痴呆、神情淡漠和反应迟钝等精神障碍，少数可有偏瘫、失语和局源性癫痫等局源性脑症状；③患者家属签署知情同意书。排除标准：①免疫功能低下；②既往有与脑部神经外科相关的手术史；③免疫功能异常及患有其他患有恶性肿瘤；④精神类疾病；⑤重要内脏器官功能障碍。将患者按照随机数表法分为对照组和观察组，63例/组，两组的一般资料具有可比性($P>0.05$)。本研究已通过我院伦理委员批准实施。

表1 两组一般资料比较[$\bar{x}\pm s$, n(%)]

Table 1 Comparison of general data between two groups[$\bar{x}\pm s$, n(%)]

Groups	Gender		Medical history			Hematoma location			CT midline shift (mm)	Hematoma volume (ML)	Age (years)
	Man	Woman	Trauma	Hypertension	Diabetes	Left	Right	Both sides			
Observation group (n=63)	30(47.62)	33(52.38)	27(42.86)	21(33.33)	15(23.81)	26(41.27)	24(38.10)	13(20.63)	6.18±1.21	56.25±2.03	65.98±2.16
Control group (n=63)	32(50.79)	31(49.21)	29(46.03)	18(28.57)	16(25.04)	23(36.51)	25(39.68)	15(23.81)	6.16±1.33	56.23±2.10	66.01±2.52
χ^2/t	0.127			0.508			0.347		0.088	0.544	0.072
P	0.722			0.776			0.841		0.930	0.957	0.943

1.2 治疗方法

两组患者均接受钻孔引流术，患者将手术区域的头发全部剃除，平卧于手术床上，标记手术切口，然后进行清洁消毒，戴手套，选用1%或者是2%的利多卡因进行局部浸润麻醉。麻醉满意后，逐层切开头皮，暴露颅骨，用颅骨电钻钻孔，钻至颅骨下硬脑膜层停止。再十字切开硬脑膜，可见血性液体流出，等到血性液体基本释放完毕，再进行冲洗。冲洗以后，留置引流管，最后逐层缝合。对照组术后用常规处理，包括包括营养支持、降血压、吸氧、清除自由基等，并及时复查头颅CT观察血肿清除情况，引流导管保留时间1~5d，无明显液体流出或CT检查显示血肿腔闭合时，则将引流管拔除。观察组患者给予口服阿托伐他汀(规格：10 mg×7片，厂家：北京嘉林药业股份有限公司，国药准字 H19990258)进行治疗，用法：每天一次，每次20 mg，连续口服1个月。

1.3 观察指标

① 血清NSE和S-100B：治疗前后在两组患者在第二日清晨空腹状态下抽取静脉血8 mL，静置20分钟后，按3000 r/min的速度离心10分钟，提取血清一式两份并冷冻保存待检，提取其中的一份，采用南京中科拜尔医学技术有限公司提供的试剂盒进行酶联免疫吸附法测定血清NSE和S-100 β 的指标水平；② 炎症因子：取用待检的一份血清，采用南京中科拜尔医学技术有限公司提供的试剂盒进行酶联免疫吸附法测定CRP、TNF- α 、IL-1的指标变化；③ MBI和CSS评分：MBI是评价日

常生活活动能力的常用康复评价标准，以评定分数的高低来区分个人生活自理能力。总分为100分，主要包括大小便、用厕、进食、转移、平地步行、穿着、上下楼梯及洗澡等项目。 >60 分，表示生活基本可以自理。 $40\sim60$ 分表示生活需要帮助才能自理。 $20\sim40$ 分表示生活需要依赖他人的帮助。 <20 分表示生活需要完全依赖他人的帮助；CSS评分总分为45分，包含水平凝视、意识水平、言语、四肢灵活度、步行能力，分数越高表示患者病情越重^[13,14]；记录不良反应、半年内对患者复查发病情况。

1.4 统计学分析

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

2 结果

2.1 两组治疗前后血清NSE和S-100B水平的比较

两组治疗后较治疗前血清NSE指标水平降低，S-100B指标水平升高，且观察组血清NSE和S-100B水平均显著低于对照组($P<0.05$)，见表2。

2.2 两组治疗前后血清炎症因子水平的比较

两组治疗后较治疗前血清CRP、TNF- α 、IL-1指标水平均降低，且观察组血清CRP、TNF- α 、IL-1水平均低于对照组($P<0.05$)，见表3。

表 2 两组治疗前后血清 NSE 和 S-100B 水平的比较($\mu\text{g/L}$, $\bar{x}\pm s$)Table 2 Comparison of the serum NSE and S-100B levels between the two groups before and after treatment ($\mu\text{g/L}$, $\bar{x}\pm s$)

Groups		NSE	S-100B
Observation group(n=63)	Before treatment	15.86±6.52	1.77±0.46
	After treatment	8.14±3.70	1.79±0.44
Control group(n=63)	Before treatment	15.83±6.49	0.26±0.09
	After treatment	12.48±4.50	0.83±0.17

Note: Compared with before treatment, * $P<0.05$; Compared with the control group, # $P<0.05$.表 3 两组治疗前后血清炎症因子比较($\bar{x}\pm s$)Table 3 Comparison of the serum inflammatory factors levels between two groups before and after treatment ($\bar{x}\pm s$)

Groups		CRP(ng/ml)	TNF- α (pg/L)	IL-1(ng/L)
Observation group(n=63)	Before treatment	9.26±0.72	110.52±6.58	9.50±0.38
	After treatment	3.47±0.45*#	70.02±4.36*#	4.13±0.29*#
Control group(n=63)	Before treatment	9.18±0.54	114.07±7.63	9.53±0.92
	After treatment	5.09±0.43*	86.29±3.85*	4.54±0.68*

Note: Compared with before treatment, * $P<0.05$; Compared with the control group, # $P<0.05$.

2.3 两组治疗前后 MBI、CSS 评分的比较

两组治疗后较治疗前 MBI 指标水平升高, CSS 指标水平

降低, 且观察组 MBI 评分高于对照组, CSS 评分低于对照组 ($P<0.05$), 见表 4。表 4 两组治疗前后 MBI、CSS 评分的比较(分, $\bar{x}\pm s$)Table 4 Comparison of the MBI and CSS scores between two groups before and after treatment(score, $\bar{x}\pm s$)

Groups		MBI	CSS
Observation group(n=63)	Before treatment	55.54±4.28	30.12±3.15
	After treatment	79.16±6.34*#	15.24±3.28*#
Control group(n=63)	Before treatment	56.48±4.30	30.10±13.13
	After treatment	63.20±7.27*	21.85±4.63*

Note: Compared with before treatment, * $P<0.05$; Compared with the control group, # $P<0.05$.

2.4 两组不良反应及复发情况的比较

两组不良反应发生率比较差异无统计学意义($P>0.05$), 观察组复发率明显低于对照组($P<0.05$), 见表 5。

表 5 两组不良反应及复发情况比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions and recurrence between the two groups [n(%)]

Groups	Infected	Intracranial emphysema	Total effective rate	Relapse rate
Observation group(n=63)	1(1.59)	1(1.59)	2(3.18)*	1(1.59)*
Control group(n=63)	2(3.18)	3(4.76)	5(7.94)	7(11.11)

Note: Compared with control group, * $P<0.05$.

3 讨论

CSDH 的出血来源和发病机制尚不完全清楚, 目前医学界认为可能是脑组织萎缩、静脉张力升高、颅内压下降等有关^[15]。在脑部遭受到外伤后, 脑膜表面的桥静脉血管损伤并出血, 血液可在硬脑膜下腔发生聚集并形成包膜, 随着时间推移, 新生的包膜会生成组织活化剂, 并释放入血肿腔, 致使新生包膜的毛细血管血浆渗出、出血等, 从而令血肿范围进一步扩大^[16,17]。患者临床表现主要为颅内压增高, 并合并明显的头痛等症状, 部分患者可出现痴呆、智力降低等精神症状, 严重者可出现丧失语言能力、偏瘫、局源性癫痫等, 甚至死亡, 对患者的生

命安全及生活质量均有着诸多不良影响^[18,19]。

临幊上对于病情稳定, 无明显神经系统症状, 无脑室受压, 血肿体积较小且中线偏移较小的患者, 通常可以采用保守治疗^[20]。对于患者病情不稳定, 存在神经系统症状, 脑室受压, 或血肿体积大于等于 30 mL, 厚度大于等于 10 mm 或中线偏移大于等于 1 cm 者, 多采取手术治疗。手术方式主要包括内镜开颅术、钻孔引流术、开颅包膜切除术^[21]。临幊实践表明由于血肿主要位于脑表面硬膜下并且血肿已经液化, 钻孔引流手术只需在颅骨上面钻孔, 打开硬脑膜即可冲洗和引流血肿, 有助于彻底清除含有炎症因子的血肿液, 并具有手术创伤小、手术时间短、效果确切、花费较低等优点, 目前钻孔引流手术目前已成为慢

性硬膜下血肿治疗的首选方法^[22,23]。但单纯的钻孔引流手术在术后恢复方面也存在不足,且有部分患者容易复发,仍需要辅助药物以促进提高疗效。

糖皮质激素是钻孔引流术后较为常用的药物,具有提高治愈率、降低复发率等效果,但此类药物需使用较大剂量,且使用时间较长,容易导致一些并发症,降低疗效。研究表明在CSDH患者发生、发展过程中,血管损伤及局部炎症反应发挥着重要作用,不仅会增加血液渗漏的发生率,还对血管生成产生阻碍作用,促进血肿增加,从而加重病情严重程度^[24]。他汀类是新一代的免疫调节剂,通过对内皮细胞功能和巨噬细胞活性的调节,从而发挥抑制内皮细胞、平滑肌细胞的生长、繁殖、转移^[25]。阿托伐他汀是他汀类药物中的代表,除具有调节血脂的功效之外,也具有较强的抑制炎症反应、促进血管生成等作用^[26]。David Yuen^[27]等研究报道指出阿托伐他汀能促进血肿包膜新生血管的成熟,并诱导血肿局部高炎状态趋于正常化,促进血肿的吸收。

研究表明CSDH患者血肿腔内的促炎因子高于外周血中的水平,且影响血肿包膜血管的新生和血管的通透性^[28]。CRP、TNF- α 、IL-1是临床评价机体炎症反应的重要指标,其表达水平越高,则代表炎症反应程度越重^[29,30]。本研究结果显示采用阿托伐他汀治疗的患者炎症因子的表达水平低于对照组,通过分析可能是由于阿托伐他汀可以抑制炎性细胞因子CRP、TNF- α 和IL-1的表达,同时其还可显著上调外周血内皮祖细胞(EPC)水平,并增加其粘附及迁移能力^[31,32]。Ratender Kumar Singh等^[33]的研究中也显示阿托伐他汀对核因子-kB通路的活性具有抑制作用,并通过此途径抑制CRP所诱导的一系列炎症反应过程,发挥炎症调控作用。

神经元特异性烯醇化酶(NSE)是反映脑组织损伤程度的敏感性指标,大量分布于脑组织,当脑细胞膜的完整性被损坏,NSE难以与脑细胞膜的肌动蛋白结合,从而通过血脑屏障进入脑部血液循环,导致脑组织中NSE水平升高。S-100B蛋白是酸性钙集合蛋白,90%以上存在中枢神经系统的星形胶质细胞当中,当中枢神经系统发生损伤时,血液和脑脊液中的S100蛋白呈现升高的状态,可用于多发性硬化症、急性脑血管病、心源性缺血缺氧性脑损伤的检测及预后的判断。本研究结果显示使用阿托伐他汀治疗的患者血清NSE和S-100B水平、CSS评分均低于对照组,MBI评分高于对照组,通过分析是由于海马体易受到系统性升高的炎症介质的影响,产生神经毒性反应,影响神经功能。而阿托伐他汀在缓解研究反应的同时,也有助于调节神经递质的释放过程,抑制小胶质细胞的激活,从而缓解继发性损伤,促进日常生活活动能力的恢复^[34,35]。本研究通过随访观察两组的复发率结果方面,使用阿托伐他汀的患者复发率为1.59%,明显比对照组患者更低,提示出在积极减少术后炎症刺激、修复神经损失后,有助于避免CSDH患者术后复发。

此外,在用药安全性方面,阿托伐他汀治疗期间,患者在不良反应和对照组比较无统计学差异,提示CSDH患者术后应用阿托伐他汀是具有安全性的,并未增加相关不良反应。但本研究仍存在着部分不足,未对考虑高血压、糖尿病对患者术后血管的影响,以及调整患者术后的日常饮食结构的方案。对于该治疗方案的长期疗效及影响等方面仍需持续探讨。

综上所述,阿托伐他汀能降低CSDH患者术后炎症反应,提高MBI、CSS评分,降低复发率,且不增加不良反应。

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