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显微外科手术对颅内动脉瘤患者脑脊液 IL-1、IL-6、ET-1、TNF- α 和 GOS 评分的影响 *

王亚飞¹ 霍龙伟^{1Δ} 郑虎林¹ 王 鹏² 白晓兵³

(1 延安大学第二附属医院(榆林市第一医院) 神经外科 陕西 榆林 719000; 2 西电集团医院 神经外科 陕西 西安 710077; 3 西安交通大学第一附属医院 神经外科 陕西 西安 710061)

摘要 目的:探讨显微外科手术对颅内动脉瘤患者的近远期疗效、安全性及对脑脊液白介素-1(IL-1)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)、内皮素-1(ET-1)水平和 GOS 评分的影响。**方法:**研究对象选取我院 2014 年 8 月到 2016 年 1 月收治的颅内动脉瘤患者 96 例,采用随机数字法将其分为对照组和观察组,每组各 48 例。对照组患者行血管内介入治疗,观察组患者行显微外科手术。比较两组患者的手术时间、术中出血量、住院时间及并发症发生情况,治疗前和治疗后 7 d 的 IL-1、IL-6、TNF- α 和 ET-1 水平,术后随访 1 年,比较两组的格拉斯哥预后评分(GOS)评分。**结果:**对照组患者的手术时间、术中出血量、住院时间及并发症发生率均明显低于观察组($P<0.01$);治疗后 7 d,观察组患者的脑脊液中 IL-1、IL-6、TNF- α 、ET-1 水平均明显低于对照组($P<0.01$);两组患者的并发症发生率比较差异无统计学意义($P>0.05$);术后一年,两组患者的格拉斯哥预后评分(GOS)比较差异无统计学意义($P>0.05$)。**结论:**显微外科手术对颅内动脉瘤的临床效果显著,能明显降低脑脊液 IL-1、IL-6、TNF- α 和 ET-1 水平,改善患者预后,且治疗安全性高。

关键词:显微外科手术;颅内动脉瘤;近远期疗效;安全性

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Effects of Microsurgery on the Levels of IL-1, IL-6, ET-1, TNF- α in Cerebrospinal Fluid and GOS of Patients with Intracranial Aneurysms*

WANG Ya-fei¹, HUO Long-wei^{1Δ}, ZHENG Hu-lin¹, WANG Peng², BAI Xiao-bing³

(1 Department of Neurosurgery, the Second Affiliated Hospital of Yan'an University (Yulin First Hospital), Yulin, Shaanxi, 719000, China; 2 Department of Neurosurgery, Xidian group hospital, Xi'an, Shaanxi, 710077, China; 3 Department of Neurosurgery, the First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, Shaanxi, 710061, China)

ABSTRACT Objective: To study the efficacy and safety of microsurgery in the treatment of intracranial aneurysms as well as the effect on cerebrospinal fluid interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and endothelin-1 (ET-1) levels. **Methods:** 96 patients with intracranial aneurysms in our hospital from August 2014 to January 2016 were selected and randomly divided into the control group and the observation group with 48 cases in each group. Patients in the control group were treated with endovascular interventional therapy, and the patients in the observation group were treated with microsurgery. The operation time, intraoperative bleeding, hospitalization time, incidence of complications, changes of cerebrospinal fluid IL-1, IL-6, TNF- α and ET-1 levels before and after the treatment, Glasgow outcome score at 1 year after surgery were compared between the two groups. **Results:** The operation time, bleeding volume, hospitalization time and the incidence of complications was significantly lower in the observation group ($P<0.01$) than those of the control group; On the 7th d after treatment, the cerebrospinal fluid IL-1, IL-6, TNF- α and ET-1 levels were significantly lower in the observation group than those of the control group ($P<0.01$); no obvious difference was found in the incidence of complications between the two groups ($P>0.05$); at one year after treatment, the Glasgow outcome score (GOS) showed no significant difference between two groups ($P>0.05$). **Conclusion:** Microsurgery had a significant effect on intracranial aneurysms, it can significantly reduce the IL-1, IL-6, TNF- α and ET-1 levels in the cerebrospinal fluid, improve the prognosis.

Key words: Microsurgery; Intracranial aneurysm; Long term effect; Safety

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前言

颅内动脉瘤是常见的脑血管疾病,具有较高的致残率和致死率^[1],是引起蛛网膜下腔出血的首要病因,同时也是继脑血

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作者简介:王亚飞(1981-),男,硕士研究生,主治医师,研究方向:胶质瘤,电话:15009126333

Δ 通讯作者:霍龙伟(1979-),硕士研究生,副主任医师,研究方向:胶质瘤,电话:18717620969

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管、高血压后,引起脑血管意外事件的第三大病因^[2],严重威胁患者生命健康。研究表明颅内动脉管壁局部先天性缺陷、腔内压力增高等因素,所致管壁局限性扩张膨出是颅内动脉瘤发病的主要原因,同时也与血管炎、高血压以及动脉硬化等因素有关。流行病学研究表明^[3]其能在任何年龄段发病,以 40~60 岁人群最为常见,青少年发病较少见。研究表明高达 90.0%以上颅内动脉瘤患者在引起动脉破裂前无明显临床症状及体征,仅有少数患者可因邻近神经和脑组织影响出现特殊临床表现,其病情危害性较高,因此,加强颅内动脉瘤早期诊断和治疗尤为重要^[4]。

目前,临床治疗颅内动脉瘤可分为非手术和手术方法,前者保守治疗为主,降颅内压、防脑血管痉挛、出血、脑脊液引流等,后者则以开颅和血管内介入为主^[5]。传统开颅手术因创伤大,手术易造成动脉瘤破裂出血,同时并发症较多,严重影响手术预后,限制其临床的开展。近年来,随着微创技术、影像学手段的发展,血管内介入和显微外科手术已成为颅内动脉瘤首先术式,颅内动脉瘤手术效果及安全性也得到明显提升,但就两种方法的有效性和安全性差异尚存在争议。因此,本研究就对两种术式治疗颅内动脉瘤的综合疗效展开比较,旨在为临床提供参考。

1 资料与方法

1.1 一般资料

研究对象选取我院 2014 年 8 月到 2016 年 1 月间收治的颅内动脉瘤患者 96 例,纳入标准^[6]:①符合 2015 年《AHA/ASA 未破裂颅内动脉瘤指南》中关于颅内动脉瘤的诊断标准;②经脑血管造影检查确诊为颅内动脉瘤;③无肝肾等器官组织疾病;④均符合血管内介入疗法和显微外科手术适应症;⑤均自愿参加并签署知情同意书。排除标准:①伴有遗传性疾病、血液系统或免疫系统严重疾病者;②肿瘤体与肿瘤颈比值小于 1.5 患者;③伴有其他颅内疾病者;④伴有其他恶性肿瘤者;⑤无手术适应症患者。采用随机数字法将其分为对照组和观察组,每组各 48 例。对照组患者男性 25 例、女性 23 例,年龄在 25~74 岁,平均年龄为(47.68±5.32)岁;观察组患者男性 24 例、女性 24 例,年龄在 23~71 岁,平均年龄为(46.98±6.56)岁。两组患者在性别、年龄等一般资料比较差异均无统计学意义($P>0.05$),故具可比性。

1.2 方法

1.2.1 血管内介入治疗 对照组患者行血管内介入治疗,术中和术中给药甘露醇以降低患者颅内压力和血压。患者气管插管全麻后,用 Seldinger 技术经股动脉插管,将导管引入颅内动脉瘤所在血管,并行数字减影血管造影(DSA),了解颅内动脉瘤

分布及形态,并选择相应电解脱铂金弹簧圈(GDC)经微导管送入动脉瘤囊并填充,再次进行 DSA 检查以判断栓塞止血效果,达预期效果后撤出导管,术后穿刺处予以盐袋压迫 6-8 h,给予患者抗凝治疗,静脉给药尼莫地平 20 mg/d,10 d,低分子肝素 3 d,并检测凝血相关指标。

1.2.2 显微外科手术 观察组患者行显微外科手术,术中和术中给予甘露醇以降低患者颅内压力及血压。患者气管插管全麻后,呈仰卧侧头位或侧卧位,采用侧裂入路,在显微镜下逐层分离组织,直至蛛网膜并沿外侧裂静脉剪开蛛网膜,分离颈动脉池、鞍上池和侧裂池,释放脑脊液,降低颅内压,若出血进入脑池则要清除其血凝块,在充分暴露载瘤动脉后,分离出动脉瘤颈部,选择合适的动脉瘤夹及夹闭角度行瘤颈夹闭术,术中注意止血,接着用罂粟碱溶液反复冲洗手术区域,放置引流管并逐层关颅,术后给予患者防止脑血管痉挛和颅内降压治疗,给药头孢、地塞米松等抗生素和甘露醇。

1.3 观察指标

1)比较两组患者的手术时间、术中出血量、住院时间;2)比较治疗前和治疗后 7 d 的脑脊液白介素 -1 (IL-1)、白介素 -6 (IL-6)、肿瘤坏死因子 - α (TNF- α)和内皮素 -1(ET-1)水平;3)比较两组患者并发症发生率;4)术后随访 1 年,比较两组的格拉斯哥预后评分(GOS)。

1.4 疗效评价标准及检测方法^[7]

治疗前后分别采集患者脑脊液 6 mL,室温下静置 20 min 后 3000 r/min 离心 15 min 后取上清液,-20℃保存待测。采用酶联免疫吸附试验(ELISA)检测 IL-1、IL-6、TNF- α 和 ET-1 水平,ET-1 试剂盒由上海广锐生物科技有限公司提供,其他均由北京方程生物科技有限公司提供,所有步骤均严格参照操作说明书进行。

参照《格拉斯哥预后量表》标准^[8]:①良好:患者生活正常,伴有轻度缺陷;②轻度残疾:伴有残疾但可独立完成基本生存操作;③重度残疾:伴有残疾,且症状严重,不能独立生存;④植物生存:仅有最小反应;⑤死亡。

1.5 统计学方法

所有统计学资料都采用 SPSS21.0 专业统计学软件进行数据分析,计量资料以均数±标准差表示,进行 t 检验,而所有的计数资料以率(n%)表示,用 χ^2 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者的手术时间、术中出血量、住院时间的比较

对照组患者的手术时间、术中出血量、住院时间均明显短于观察组($P<0.01$),详情见表 1。

表 1 两组患者的手术时间、术中出血量、住院时间比较($\bar{x}\pm s$)

Table 1 Comparison of operation time, intraoperative blood loss, hospitalization time in the two groups($\bar{x}\pm s$)

Groups	Operation time (min)	Intraoperative blood loss (mL)	Hospitalization time (d)
Observation group(n=48)	128.65±19.45	142.51±27.25	17.25±4.89
Control group(n=48)	85.32±15.82	92.25±16.48	12.41±5.24
P	0.00	0.00	0.00

2.2 两组患者治疗前及治疗后 7d 脑脊液的 IL-1、IL-6、TNF- α 、ET-1 水平比较

治疗前, 两组患者的脑脊液中 IL-1、IL-6、TNF- α 、ET-1 水

平比较差异无明显统计学意义($P>0.05$); 治疗后 7d, 观察组患者的脑脊液中 IL-1、IL-6、TNF- α 、ET-1 水平均明显低于对照组($P<0.01$), 详情见表 2。

表 2 两组患者治疗前及治疗后 7d 的脑脊液 IL-1、IL-6、TNF- α 、ET-1 水平比较($\bar{x} \pm s$)

Table 2 Comparison of the IL-1, IL-6, TNF- α , ET-1 levels in cerebrospinal fluid before and on the 7th day after treatment between the two groups($\bar{x} \pm s$)

Groups	IL-1(pg/mL)		IL-6(pg/mL)		TNF- α (pg/mL)		ET-1(pg/mL)	
	Before treatment	On the 7th day after treatment	Before treatment	On the 7th day after treatment	Before treatment	On the 7th day after treatment	Before treatment	On the 7th day after treatment
Observation group(n=48)	203.2 $\pm$ 52.4	132.68 $\pm$ 39.85 [°]	363.52 $\pm$ 77.25	169.56 $\pm$ 48.62 [°]	438.59 $\pm$ 78.32	262.52 $\pm$ 58.32 [°]	26.25 $\pm$ 6.21	16.54 $\pm$ 3.25 [°]
Control group(n=48)	205.5 $\pm$ 49.8	179.65 $\pm$ 42.25 [°]	362.24 $\pm$ 76.98	231.62 $\pm$ 58.62 [°]	439.52 $\pm$ 76.98	319.85 $\pm$ 62.15 [°]	26.58 $\pm$ 6.58	24.32 $\pm$ 4.25 [°]
P	0.14	0.00	0.18	0.00	0.22	0.00	0.15	0.00

Note: [°] compared with before treatment, $P<0.05$.

2.3 两组患者并发症发生情况的比较

对照组患者颅内感染、切口感染、电解质紊乱、脑血管痉挛

等并发症发生率为 10.42%, 观察组并发症总发生率为 12.50%, 两组患者比较无差异明显($P>0.05$), 详情见表 3。

表 3 两组患者并发症发生情况的比较(n%)

Table 3 Comparison of the incidence of complications between the two groups (n%)

Groups	Intracranial infection	Incision infection	Electrolyte disturbance	Cerebral vasospasm	Total rate
Observation group(n=48)	2(4.17)	0(0)	2(4.17)	1(2.08)	5(10.42)
Control group(n=48)	2(4.17)	1(2.08)	1(2.08)	2(4.17)	6(12.50)
P			-		0.80

2.4 术后随访 1 年, 两组患者 GOS 评分的比较

两组患者的良好率、轻度残疾率、重度残疾率、植物生存率、

死亡率比较差异均无明显统计学意义($P>0.05$), 详情见表 4。

表 4 两组患者术后随访 1 年时 GOS 评分比较(n%)

Table 4 Comparison of the GOS score between the two groups (n%)

Groups	Good	Mild disability	Severe disability	Plant survival	Death
Observation group(n=48)	36(75.00)	4(8.33)	3(6.25)	3(6.25)	2(4.17)
Control group(n=48)	35(72.92)	5(10.42)	4(8.33)	2(4.17)	2(4.17)
P	0.82	0.77	0.85	0.79	1.00

3 讨论

颅内动脉瘤随着体积增大则压迫周围脑组织, 若压迫动眼神经可引起斜视、眼球活动障碍, 压迫三叉神经可引起前额疼痛, 压迫语言中枢严重可导致失语^[9]。当体积过大时则会引起颅内压增高, 患者出现头痛、呕吐等症状^[10]。近年来, 有关学者发现颅内动脉瘤的发生发展可能与免疫炎症反应有相关^[11], 并认为炎症细胞可能通过分泌炎症细胞因子参与颅内动脉瘤的形成与发展。目前, 越来越多的研究证实^[12,13]颅内细胞瘤瘤壁中存在巨噬细胞、淋巴细胞浸润, 并推测当脑血管受到损伤时炎症细胞如巨噬细胞、淋巴细胞等浸润到血管壁, 并分泌炎症细胞因子和蛋白水解酶, 对血管壁造成继发性损伤, 引起血管基质细胞和平滑肌细胞加速凋亡, 导致瘤样膨出。

核因子- κ B (NF- κ B) 是一种介导炎症反应的重要转录因子, 可调节多种炎症介质如 TNF- α 、IL-1、IL-6 等的表达, 从而加重血管炎症促进颅内动脉瘤的生成^[14]。TNF- α 是一种能在体外杀死肿瘤细胞或者注射入肿瘤内会导致肿瘤出血坏死的单核因子, 其主要作用是引发炎症反应及免疫反应, 作用位点多为血管内皮细胞^[15]。有研究表明^[16]TNF- α 可能是通过 NF- κ B 途径促发炎症反应, 同时在炎症反应中 TNF- α 与 IL-1、IL-6 呈协同作用。IL-1、IL-6 均为白介素家族成员, 均有调节免疫应答, 促进炎症反应的作用。IL-1 基因呈现多态性, 与动脉瘤形成密切相关, IL-1 的释放可抑制内皮细胞的增殖, 诱导其表达粘性分子, 从而诱发动脉瘤^[17]。IL-6 是多靶位细胞因子, 可引起血管壁变薄、脆性增加, 加重炎症反应等^[18], 从而增加动脉瘤发病率。ET-1 是具有强烈收缩血管作用的细胞因子^[19], 在脑组织中

可以产生,与脑血管痉挛密切相关。

目前,颅内动脉瘤有保守治疗和手术治疗两种方法。随着介入治疗的发展,血管内介入术因其创伤小、痛苦轻、恢复快、安全性高等优点广泛应用于颅内动脉瘤的临床治疗^[20]。但有研究显示^[21]该治疗使用的弹簧圈若进入动脉瘤则会造成动脉瘤闭塞、痉挛甚至破裂等则造成严重后果,且该治疗方法将患者暴露于辐射环境中,可能对患者其他器官造成不可逆伤害,同时血管介入术的治疗费用昂贵,不适合全部人群。显微外科手术在直视下解剖,充分打开脑池,可清除蛛网膜下腔积血、颅内血肿,有效降低颅内压,防止动脉瘤破裂出血^[22];打开终板,可减少脑积水和血管痉挛等并发症的发生率,手术疗效确切,被广泛应用于临床,为目前根治颅内动脉瘤的主要方法^[23]。目前,有研究显示显微外科手术对颅内血管瘤附近脑组织可能会造成牵拉性损伤^[24],提示显微外科手术患者创伤因子水平明显高于血管介入术。同时,该研究指出显微外科手术患者机体炎症因子水平明显低于血管介入术。本研究结果显示:对照组患者的手术时间、术中出血量、住院时间明显低于观察组,表明血管内介入治疗相较于显微外科手术更便捷,术中安全性更高;两组患者的并发症发生率比较无明显差异,表明两种治疗方法效果相近,整体安全性相近^[25];同时,研究显示治疗后 7d 观察组患者的脑脊液中 IL-1、IL-6、TNF- α 、ET-1 水平明显低于对照组,表明显微外科手术治疗后患者机体的炎症反应较低,更利于患者的恢复。此外,本研究也显示两组患者的格拉斯哥预后评分(GOS)比较无明显差异,表明血管内介入治疗与显微外科手术治疗远期疗效相当,与目前研究一致^[26]。

综上所述,显微外科手术对颅内动脉瘤的临床效果显著,能明显降低脑脊液 IL-1、IL-6、TNF- α 和 ET-1 水平,改善患者预后,且治疗安全性高。

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