

银杏二萜内酯葡胺注射液对急性缺血性脑卒中再通成功患者预后的影响

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摘要: **目的** 观察银杏二萜内酯葡胺注射液(DGMI)对急性缺血性脑卒中(AIS)再通成功患者预后的影响。**方法** 回顾性选取南京大学医学院附属鼓楼医院和南京医科大学第一附属医院2016年6月—2021年12月收治的AIS再通治疗患者为研究对象,共纳入颈内动脉或大脑中动脉闭塞者206例。根据再通治疗后3 d头颅磁共振血管造影(MRA)检查结果,将206例患者分为开通成功患者($n=157$,其中61例接受DGMI治疗)和开通失败患者($n=49$,其中21例接受DGMI治疗);以患者是否接受过DGMI治疗为依据,将接受DGMI治疗 ≥ 7 d的患者设为试验组($n=82$),未接受DGMI治疗的为对照组($n=124$)。收集的临床资料包括年龄、性别、发病至干预时间、干预方式、不良事件(症状性脑出血、死亡)、发病时和90 d的美国国立卫生研究院卒中量表(NIHSS)评分和改良Rankin评分量表(mRS)评分。分别比较开通成功患者和开通失败患者中对照组和试验组间不良事件发生率和预后的差异,包括症状性脑出血率、死亡率,以及90 d后的NIHSS改善率和mRS评分。**结果** 开通成功患者中,试验组90 d NIHSS改善率和mRS评分均明显优于对照组($P<0.05$);而在开通失败患者中两组间90 d NIHSS改善率和mRS评分比较,差异无统计学意义($P>0.05$);对照组和试验组的症状性脑出血率和死亡率在两组中均无明显差异($P>0.05$)。**结论** 对于接受再通治疗的AIS患者,DGMI有利于再通成功患者的神经功能改善,且不增加不良事件发生风险。

关键词: 银杏二萜内酯葡胺注射液;急性缺血性脑卒中;再通治疗;美国国立卫生研究院卒中量表;改良Rankin评分量表
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Effect of Diterpene Ginkgolides Meglumine Injection on prognosis of patients with successful recanalization of acute ischemic stroke

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Abstract: Objective To study the effect of Diterpene Ginkgolides Meglumine Injection(DGMI) on the prognosis of patients with successful recanalization of acute ischemic stroke (AIS). **Methods** A total of 206 patients with internal carotid artery or middle

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cerebral artery occlusion who were admitted to the Nanjing Drum Tower Hospital Affiliated Hospital of Nanjing University Medical School and the First Affiliated Hospital of Nanjing Medical University from June 2016 to December 2021 were selected as the study subjects. According to the results of skull magnetic resonance angiography (MRA) three days after recanalization treatment, 206 patients were divided into two groups: successful patients ($n = 157$, of which 61 were treated with DGMI) and failed patients ($n = 49$, of which 21 were treated with DGMI). Based on whether the patients have received DGMI treatment, the patients who have received DGMI treatment for ≥ 7 days are set as the experimental group ($n = 82$), and the patients who have not received DGMI treatment are set as the control group ($n = 124$). The clinical data collected included age, sex, time from onset to intervention, intervention mode, adverse events (symptomatic cerebral hemorrhage, death), the National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin Scale (mRS) score at the time of onset and 90 days. The difference in the incidence of adverse events and prognosis between the control group and the experimental group, including the rate of symptomatic intracerebral hemorrhage, mortality, and the improvement rate of NIHSS and mRS score after 90 days, were compared between the patients with successful and failed opening. **Results** The improvement rate of NIHSS and mRS score in the experimental group at 90 days were significantly better than those in the control group ($P < 0.05$). However, there was no significant difference between the two groups in the improvement rate of NIHSS and mRS score at 90 days in patients with failed opening ($P > 0.05$). There was no significant difference in the rate of symptomatic intracerebral hemorrhage and mortality between the two groups ($P > 0.05$). **Conclusion** For AIS patients receiving recanalization treatment, DGMI is beneficial to the improvement of neurological function in patients with successful recanalization without increasing the risk of adverse events.

Key words: Diterpene Ginkgolides Meglumine Injection; acute ischemic stroke; recanalization therapy; National Institutes of Health Stroke Scale; modified Rankin Scale

脑卒中是导致人类致死、致残的主要疾病之一,其中,急性缺血性脑卒中(AIS)是其最主要的类型,占有脑卒中的80%^[1],我国AIS患者每年的致死率/致残率为33.4%~44.6%^[2-3]。AIS再通治疗,包括静脉溶栓和血管内介入治疗,是AIS非常重要的治疗措施,可有效减少该类患者的致残率^[4-5]。尽管如此,再通治疗的效果仍有很大的不确定性。研究结果显示,约有40%的AIS患者再通治疗后神经功能显著改善,但仍有部分患者无法从中获益,甚至发生症状性脑出血^[6]。影响AIS再通患者预后的因素很多,其中缺血再灌注损伤是因素之一。随着血供的恢复,缺血区氧自由基生成过多,造成炎症因子释放并诱发炎症级联反应,最终对缺血区造成氧化应激和炎症损伤^[7]。银杏二萜内酯葡胺注射液(diterpene ginkgolides meglumine injection, DGMI)是由银杏叶提取物制成的中药注射液,其有效成分银杏二萜内酯A、B、K等可用于治疗AIS,具有拮抗血小板活化因子受体、清除氧自由基、抑制炎症反应等作用,从而保护缺血脑组织对抗再灌注损伤^[8-9]。既往研究认为DGMI可改善经静脉溶栓治疗的AIS患者的神经功能,进而改善患者预后^[10]。临床上AIS患者虽经再通治疗,其责任血管并不能保证一定开通成功,同时开通成功率也不一致,比如相较于红细胞富集血栓,纤维素富集血栓无论溶栓还是介入的清除效果都要差很多^[11],这就造成在分析预后时难免出现偏差。本课题组在以往的研

究中注意到该问题,就曾将AIS再通的纳入标准设为明确责任血管开通成功者^[12]。本研究对以往收治的AIS再通患者进行回顾性分析,旨在探讨DGMI对AIS再通患者预后的影响。严谨起见,纳入的病例进一步评估责任血管是否开通成功,具体由再通治疗后3 d头颅磁共振血管造影(MRA)检查结果判定。本研究为DGMI的脑保护相关研究提供资料,并探讨其可能的机制。

1 资料与方法

1.1 一般资料

本项多中心回顾性研究分别由南京大学医学院附属鼓楼医院急诊科和南京医科大学第一附属医院急诊科收集病例,两家机构在急诊科设立卒中绿色通道,对AIS患者进行再通治疗(包括静脉溶栓和介入取栓),并开展合作。本课题组的研究资料来源于2016年6月—2021年12月南京大学医学院附属鼓楼医院和南京医科大学第一附属医院的卒中绿色通道数据库。进入通道的患者首先进行头颅CT及CT灌注(CTP)排查,符合条件者在卒中医师充分评估下给予静脉溶栓和(或)介入治疗。具体溶栓和介入适应证和禁忌证参考《中国急性缺血性脑卒中诊治指南2014》^[13]和《急性缺血性卒中血管内治疗中国指南2015》^[14]。具体溶栓方案为,阿替普酶作为溶栓药,总剂量按 $0.9 \text{ mg} \cdot \text{kg}^{-1}$ 计算,先将10%药量静脉推注5 min,余下药量静脉维持1 h。符合介入指征的患者,无论是否静脉溶栓,都安排

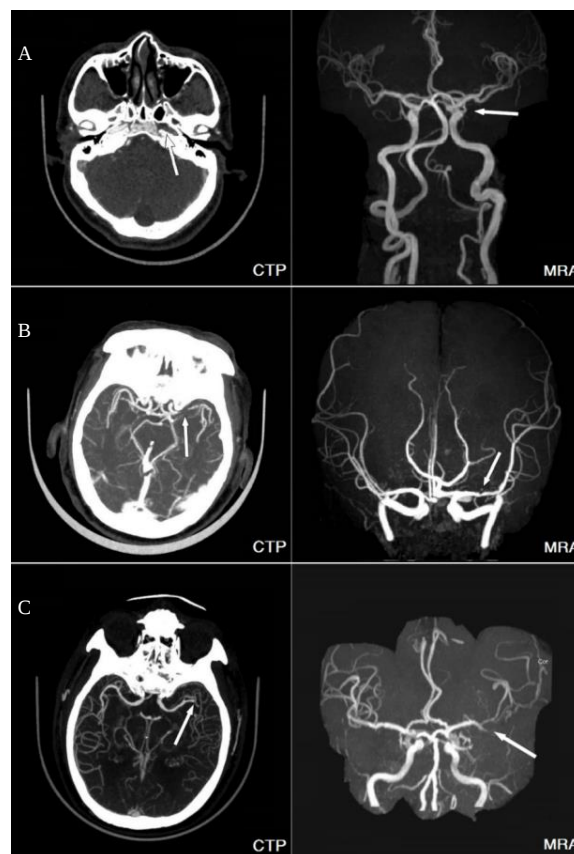
介入治疗。所有接受再通治疗的AIS患者,继续住院接受内科药物治疗,包括抗血小板聚集、稳定斑块、营养神经,以及其他对症支持治疗。2018年2月DGMI(江苏康缘药业股份有限公司,国药准字Z20120024)被引进,并用于AIS再通患者的治疗。再通治疗后第1、3天分别进行头颅CT和头颅MRA检查,症状加重则随时复查头颅CT,明确是否有症状性脑出血,以及责任血管是否开通成功。定期随访90 d,给予美国国立卫生研究院卒中量表(NIHSS)评分和改良Rankin评分量表(mRS)评分。

1.2 资料分析

本研究旨在探讨DGMI分别对AIS再通成功和失败患者的影响,为保证研究资料的可比性和责任血管开通评估的准确性,课题组选择前循环闭塞的AIS患者进行研究。具体入组标准为:①CTP提示颈内动脉或大脑中动脉闭塞;②接受了静脉溶栓和(或)介入取栓治疗;③发病时NIHSS评分5~20分;④年龄18~80岁。排除标准为:①既往疾病遗留神经功能缺失;②既往存在严重的心肺不全;③资料不全。自DGMI于2018年2月被引入后,AIS再通患者在住院期间开始接受DGMI治疗(25 mg加入250 mL生理盐水缓慢静脉滴注,每天1次)。按该时间点将之前患者设为对照组,将之后接受过DGMI治疗,且 ≥ 7 d的患者设为试验组,用药疗程不足,按资料不全排除。以此标准,共有206例患者纳入研究,对照组和试验组患者分别为124例、82例。以再通后3 d的头颅MRA结果作为开通成功与否的标准:MRA显示责任血管狭窄或通畅者被认为开通成功,显示责任血管闭塞者被认为开通失败,见图1。开通成功患者和开通失败患者分别为157例(其中61例接受DGMI治疗)、49例(其中21例接受DGMI治疗)。收集的临床资料包括年龄、性别、发病至干预时间、干预方式、不良事件(症状性脑出血、死亡)、发病时和90 d的NIHSS、mRS。90 d NIHSS改善定义为随访90 d患者的NIHSS评分较发病时提高 >4 分^[15-16]。干预方式包括静脉溶栓、介入取栓,以及静脉溶栓衔接介入治疗。发病至干预时间定义为从出现卒中症状到首次给予阿替普酶静脉输注或介入经皮穿刺的时间。

1.3 统计学分析

采用SPSS 11.5软件进行统计分析,计量资料以 $\bar{x} \pm s$ 表示,两组间比较采用 t 检验;计数资料以构成比或百分率表示,两组间比较采用 χ^2 检验、校正 χ^2 或



A-治疗前 CTP 显示左颈内动脉 C1-4 闭塞,干预后 3 d MRA 显示原闭塞部位通畅,判为开通成功;B-治疗前 CTP 显示左大脑中动脉 M1 近端闭塞,干预后 3 d MRA 显示原闭塞部位轻度狭窄,远端灌注良好,判为开通成功;C-治疗前 CTP 显示左大脑中动脉 M2 近端闭塞,干预后 3 d MRA 显示原闭塞部位仍闭塞,远端分支显影不良,判为开通失败;箭头-责任血管的闭塞部位

A-It was judged as successful recanalization while CTP showed left internal carotid artery C1-4 occlusion before treatment, and MRA showed that original occlusion site was unobstructed after three days of recanalization treatment; B-It was judged as successful recanalization while CTP showed that proximal end of left middle cerebral artery M1 was occluded before treatment, and MRA showed that original occlusive site was slightly narrowed and distal perfusion was good after three days of recanalization treatment; C-It was judged as failure while CTP showed proximal occlusion of left middle cerebral artery M2 before treatment, and MRA showed that original occluded site was still occluded and distal branch was poorly developed after three days of recanalization treatment; Arrow-occluded part of responsible vessel

图1 头颅MRA对开通成功与否的评估

Fig. 1 Assess of successful recanalization according to results of cranial MRA

Fisher精确检验。以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者临床特征比较

两组患者一般情况、发病时神经功能、开通干预措施相比较均无统计学差异($P > 0.05$),提示两组具有可比性。此外,两组患者不良事件,如症状性

脑出血和死亡,90 d NIHSS改善和mRS,相比无显著差异($P>0.05$)。见表1。

2.2 DGMI对AIS再通患者不良事件的影响

按开通成功与否,将入组的AIS患者分成开通成功患者和开通失败患者,分别在两类患者中分析DGMI对AIS不良事件的影响,结果见表2。无论是否开通成功,DGMI对AIS不良事件未表现出显著的影响,试验组和对照组的症状性脑出血、90 d死亡率均无明显差异($P>0.05$)。

2.3 DGMI对AIS再通患者90 d NIHSS改善率的影响

开通成功患者中,试验组90 d NIHSS改善率较

对照组明显提高,差异有统计学意义($P<0.05$);而在开通失败患者中,两组90 d NIHSS改善率无显著差异($P>0.05$)。见图2。

2.4 DGMI对AIS再通患者90d mRS的影响

开通成功患者中对照组和试验组90 d mRS评分分别是 2.34 ± 1.42 、 1.85 ± 1.48 ,试验组明显低于对照组($P<0.05$);开通失败患者中对照组和试验组90 d mRS评分分别是 2.43 ± 1.64 、 2.38 ± 1.69 ,两组间比较差异无统计学意义($P>0.05$)。各组中mRS评分分值占比见图3。

表1 两组患者临床特征比较

Table 1 Comparison of clinical characteristics of patients between two groups

临床资料	对照组($n=124$)	试验组($n=82$)	t/χ^2 校正 χ^2	P 值
年龄/岁	66.5 ± 10.1	65.5 ± 9.7	0.932	0.443
性别/例(男/女)	(59/65)	(49/33)	2.934	0.087
干预措施 仅静脉溶栓/例(占比/%)	42(33.9)	23(28.0)	0.775	0.379
仅介入取栓/例(占比/%)	34(27.4)	27(32.9)	0.718	0.397
静脉溶栓衔接介入/例(占比/%)	48(38.7)	32(39.0)	0.002	0.964
发病至干预时间/min	336.9 ± 90.1	316.5 ± 89.1	-1.604	0.110
症状性脑出血/例(占比/%)	8(6.5)	6(7.3)	0.058	0.809
开通成功/例(占比/%)	96(77.4)	61(74.4)	0.250	0.617
开通成功患者 发病时 NIHSS	13.0 ± 4.5	14.0 ± 4.7	1.371	0.172
发病时 mRS	2.98 ± 1.21	3.08 ± 1.08	0.541	0.589
开通失败患者 发病时 NIHSS	12.8 ± 3.9	13.1 ± 4.5	0.324	0.747
发病时 mRS	3.07 ± 1.30	2.95 ± 1.28	-0.318	0.752
所有患者发病时 NIHSS	12.9 ± 4.4	14.0 ± 4.7	1.617	0.107
所有患者发病时 mRS	3.00 ± 1.22	3.04 ± 1.13	0.289	0.773
90 d 预后 NIHSS 改善/例(占比/%)	42(35.5)	36(43.9)	2.111	0.146
mRS 评分	2.05 ± 1.49	2.42 ± 1.40	-1.810	0.072
死亡/例(占比/%)	5(4.0)	2(2.4)	0.051	0.822

表2 不良事件发生率比较

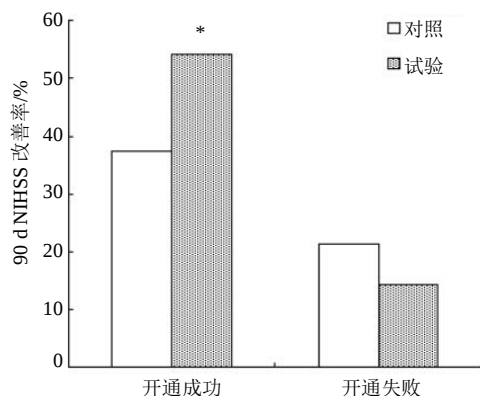
Table 2 Comparison of adverse event incidence

不良事件	开通成功患者($n=157$)			开通失败患者($n=49$)		
	对照组($n=96$)	试验组($n=61$)	P 值	对照组($n=28$)	试验组($n=21$)	P 值
症状性脑出血/例(占比/%)	6(6.3)	5(8.2)	0.885	2(7.1)	1(4.8)	1.000
90 d 死亡/例(占比/%)	4(4.2)	2(3.3)	1.000	1(3.6)	0(0)	1.000

3 讨论

脑血管再通治疗是AIS的非常有效的救治措施,包括静脉溶栓和血管内介入治疗。AIS发生早期,脑缺血区域包括梗死核心区 and 缺血半暗区^[17]。前者的脑组织死亡不可逆,而后者脑组织若及时获得血供,将有机会逆转死亡进程,对缺失的神经功

能恢复有着重要意义^[17]。但既往研究发现,即使在时间窗内接受再通治疗,部分患者的神经功能并未及时恢复,本课题组就曾报道,部分AIS溶栓患者的疗效存在滞后性,表现为溶栓数日甚至数周后神经功能才得以改善,推测其原因可能为“缺血神经元顿抑”,即血管开通后存活的脑细胞早期处于无功



与对照组比较: * $P < 0.05$

* $P < 0.05$ vs control group

图2 两组 90 d NIHSS 改善率比较

Fig. 2 Comparison of NIHSS improvement rate in 90 days between two groups

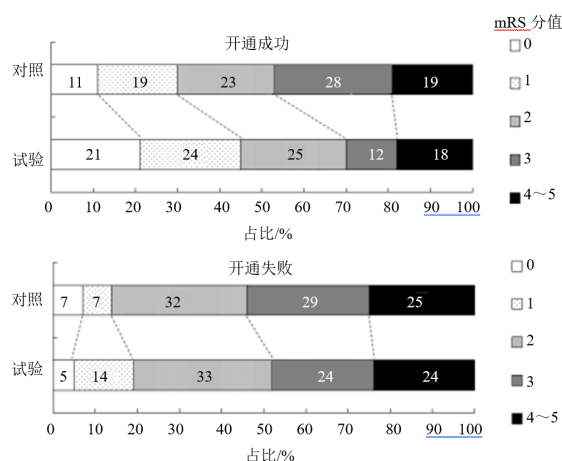


图3 mRS 分值在每组患者中的占比

Fig. 3 Proportion of mRS score in patients in each group

能状态,而这部分“冬眠”的脑细胞需要存活下来并发挥功能^[18]。因此,迅速开通责任血管是治疗的第一步,对这些“冬眠”的脑细胞的保护也不容忽视。GDLM是近些年来研发的一种新型中药制剂,具有活血通络的作用。以往研究发现,其所包含的单体如银杏二萜内酯A、B和K,可通过抑制缺血神经元的氧化应激、炎症反应和凋亡等,从而保护脑细胞^[19-21]。

缺血受损的脑组织在恢复血供后,经血流的冲击易引发出血风险。GDLM具有活血化瘀、抑制血小板聚集的作用,而在本研究中,试验组的症状性脑出血发生率并未明显增加,90 d的死亡率也与对照组结果类似,提示GDLM没有促进不良事件的发生,具有相当的安全性,与以往研究结论相类似^[22]。此外,本研究还发现,在开通成功的AIS患者中,试验组90 d NIHSS改善率较对照组显著提高,mRS评

分也出现明显下降,提示GDLM可改善AIS再通患者的预后。推测可能机制如下:开通闭塞血管可以使脑缺血区恢复血供,但并不意味着存活脑细胞此后万无一失,它们将面对缺血/再灌注损伤。其损伤机制可能与氧化应激和炎症反应有关,加重脑细胞损伤甚至引起凋亡。以往研究表明,活性氧(ROS)产生的氧化应激是造成脑细胞凋亡的重要环节^[23-24]。体外实验显示,GDLM可减少体外缺血神经元的ROS的产生,抵抗氧化应激损伤;可通过下调calpain信号通路,抑制缺糖氧复糖氧神经元凋亡,具有神经元保护作用^[25-26]。既往研究发现,脑组织缺血再灌注后早期即可出现白细胞聚集及细胞因子产生和释放增多,如白细胞介素-1(IL-1)、IL-6等。IL-1可介导核因子- κ B(NF- κ B)、磷酸化P38丝裂原活化蛋白酶等通路,诱导神经元凋亡。仲崇金等^[27]报道在脑缺血急性期,GDLM能增强超氧化物歧化酶的活力,降低丙二醛和IL-1 β 、IL-6的水平,减轻氧化应激和抑制炎症反应,促神经功能恢复。罗燕平等^[28]在大鼠模型上发现GDLM可修复血脑屏障,减少脑脊液兴奋性氨基酸的产生,减轻急性脑梗死大鼠神经损伤症状。故在本研究中,GDLM可能通过对抗缺血/再灌注损伤,发挥脑保护作用,进而促进了开通成功的AIS患者神经功能恢复。最后,本研究还发现,GDLM对开通失败的AIS患者的预后改善没有帮助,两组的90 d NIHSS改善率和mRS未见统计学差异。以往有报道指出,GDLM对未接受开通治疗的AIS患者也有改善预后的作用^[29],这与本研究结果有出入。具体原因尚不清楚,推测可能与本研究开通失败患者病例数相对较少有关。

本研究显示GDLM的疗效与AIS患者责任血管开通成功与否有关,相对于开通失败者,开通成功者更有可能从GDLM的治疗中获益。此外需指出的是,本研究尚存在一些不足,如历史对照研究的质控,开通失败AIS患者样本量较少,观察终点只有90 d等。GDLM对AIS患者的保护作用和具体机制,尚待后续更多样本量的相关临床研究,以及基础研究的深入。

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