

. 综 述 .

尼莫地平在 aSAH 治疗中的研究进展

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【关键词】 颅内动脉瘤;蛛网膜下腔出血;尼莫地平;脑血管痉挛

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自发性蛛网膜下腔出血(subarachnoid hemorrhage, SAH)主要由颅内动脉瘤破裂引起,脑血管痉挛(cerebral vasospasm, CVS)、迟发性脑缺血(delayed cerebral ischaemia, DCI)是动脉瘤性SAH(aneurysmal SAH, aSAH)致残和死亡的主要原因^[1-3]。早期、积极预防这些并发症有助于改善患者预后。Meta分析表明,尼莫地平降低aSAH患者CVS、DCI、迟发性神经缺失发生率,明显改善患者预后^[3,4]。本文就尼莫地平在aSAH治疗中研究进展进行综述。

1 尼莫地平给药方式与疗效

1.1 口服和静脉注射 口服和静脉注射是尼莫地平传统的给药方式。大部分随机临床研究以尼莫地平口服给药,只有小部分研究以静脉注射给药^[3-5]。尼莫地平口服给药能明显改善aSAH患者预后^[5]。Liu等^[4]纳入8篇文献荟萃分析,含1 514例aSAH,与安慰剂组对比,口服尼莫地平可明显降低病死率、重残和植物生存状态发生率,明显降低症状性CVS发生率、脑梗死发生率、迟发性神经功能缺失发生率。

口服和静脉注射尼莫地平对aSAH患者均可达到良好预期效果^[4],口服的效果更明显。研究发现,成人口服尼莫地平低血压并发症少见;但是儿童口服尼莫地平低血压并发症突出,而且不能降低颅内出血、CVS、脑梗死等发生率^[6]。

1.2 动脉内给药 动脉内注射扩血管药物的装置是由4F、5F鞘和微导管等组成,通过微导管将一定剂量的尼莫地平送入痉挛血管处,使痉挛血管扩张。Ott等^[7]对30例aSAH至严重CVS患者给予动脉内尼

莫地平注射,结果发现83%的患者有良好的临床预后,23%的患者完全康复;还发现GOS评分1~3分患者100%存在持续性局部缺血,而GOS评分4~5分患者的比例只有69%。尼莫地平动脉内注射只需要小剂量即可明显扩张颅内痉挛血管^[8],明显改善患者临床预后,而没有严重并发症发生^[9]。

aSAH患者CVS接受动脉内尼莫地平给药技术(intra-arterial nimodipine angioplasty, IANA)与球囊辅助成形术(transluminal balloon angioplasty, BA)治疗的临床预后没有显著差异^[10]。BA被推荐为治疗近段及间断性CVS^[10],而IANA可扩张远端细小痉挛血管,但是效果是短暂性的。最近,有研究显示,SAH后CVS接受IANA治疗有明显良好的临床预后^[7,8,10],IANA可提高患者局部脑血流量^[7],降低DCI和脑梗死的发生率^[7,10,11]。IANA潜在风险有血管破裂、迟发性低血压、过敏性皮疹、空气栓塞、血栓栓塞、微导管打结及血栓形成、败血症等^[8]。荟萃分析表明,IANA对SAH后难治性CVS是一种有效、快速、安全的血管内治疗方法^[7-9]。

2 尼莫地平剂量与效果相关性

痉挛血管内非常低浓度的尼莫地平有非常强的扩血管作用,因此,对aSAH后CVS患者在血管内应用尼莫地平治疗有明显的优点;同时,尼莫地平扩血管作用的降低是因为血管的结构改变^[9]。痉挛血管中尼莫地平最有效的浓度范围为1~100 nmol/L,在这个范围中,随着浓度的增加血管扩张也越明显;但是超过100 nmol/L后扩血管的作用明显降低^[9]。

3 尼莫地平缓慢释放技术

含有尼莫地平的聚乳酸/聚乙醇酸共聚物(polylactic-co-glycolic acid, PLGA)微颗粒悬浮在薄层纤维蛋白密封剂中,是一套缓慢释放尼莫地平系统^[12]。尼莫地平EG-1962微颗粒是尼莫地平PLGA

微颗粒中的一种,可持续缓慢释放尼莫地平长达21 d;优点是克服传统给药方式的反复多次、持续注射、技术难、侵害性、低血压等^[13]。将持续释放尼莫地平小球放置在aSAH患者侧裂池血管周围,可明显降低DCI的发生率,并提高aSAH患者临床预后^[12,13]。一项将二氧化硅为载体持续释放尼莫地平系统植入到SAH猪的颅内,由于尼莫地平的持续释放,在脑脊液中形成高浓度尼莫地平,被推荐为治疗SAH后CVS和DCI的有效措施;同时,在植入物周围没有发现有脑组织损伤和异物免疫排斥反应^[14]。与传统治疗给药方法比较,尼莫地平持续释放系统对患者有明显的优点和尼莫地平非常高的利用率^[14]。

传统的口服、静脉注射、动脉注射等给药技术降低aSAH毒副作用,提高aSAH患者临床预后^[7,8];但是,反复给药、持续注射、技术难度大、有创性、低血压等是传统给药技术缺陷^[7,8,11,15]。尼莫地平缓慢释放技术可解决上述一些缺点^[13]。因此,尼莫地平PLGA微粒、尼莫地平二氧化硅粒等尼莫地平缓慢释放系统被推荐治疗aSAH^[12,14]。

4 尼莫地平的治疗机制

4.1 aSAH毒副作用 SAH对患者的毒副作用原因还没有研究清楚^[16]。DCI引起迟发性梗死,没有足够的血供和营养予脑组织,导致脑神经功能永久的缺失,发生严重的临床症状^[1,3,4]。传统观点认为,CVS通过DCI来引起严重的临床症状。然而,CVS和迟发性脑梗死有明显的相关性^[1,3,4]。因此,颅内痉挛血管的扩张是系统性治疗aSAH的重要目标^[1]。但是,CVS和DCI缺乏一致性,脑血管造影和脑灌注成像研究发现CVS和脑灌注不足存在不一致性。因此,除了CVS,脑血管自动功能的调节紊乱、皮层扩散抑制、微血栓形成、血小板聚集、炎症等也是形成DCI的重要原因^[1,2]。动脉壁的平滑肌表型改变与脑大动脉、微血管有关^[16]。动脉壁平滑肌收缩痉挛原因之一,L-type钙通道兴奋^[17];然而,血管痉挛与血管平滑肌对二氢吡啶敏感性降低密切相关^[18]。

4.2 尼莫地平扩血管机制 应用尼莫地平可明显减少aSAH后CVS^[9,11,15,19]。SAH后脑血管的电压钙通道较正常脑血管明显改变,当脑血管的电压钙通道表达增高,尼莫地平可能丧失扩血管功能^[17],表明尼莫地平是通过抑制脑血管的电压钙通道表达来扩张血管。电压钙通道阻滞剂SNX-482可抑制脑血流量的下降^[20]。L-型钙通道表达增高可导致大动脉血管痉挛^[18]。在SAH患者中,TRPC1、STIM1、储存组件

钙通道可调节血管平滑肌上钙离子流入和表型转换,明显改善CVS^[21]。R-型钙通道阻滞剂可明显提高aSAH患者脑血流量^[20]。

4.3 尼莫地平其他机制 尼莫地平改善aSAH患者临床预后不仅是降低CVS发生率^[11,15],而且还抑制微循环功能失调,降低DCI和脑梗死发生率^[3,4]。

4.4 尼莫地平作用机制与传统观点矛盾 现在许多研究与我们传统尼莫地平对aSAH患者有利观点矛盾。研究表明尼莫地平对aSAH患者病死率、迟发性神经损伤无效,原因可能是尼莫地平不可持续减少脑梗死^[3,4]、微循环功能紊乱、炎症反应^[18],没有改善CVS^[7,8]、脑血流量^[8]。因此,尼莫地平在什么情况下才是对aSAH患者最有保护作用有待进一步研究。

总之,尼莫地平对aSAH患者保护作用机制还不清楚。口服尼莫地平对aSAH患者疗效肯定,血管内局部低浓度尼莫地平对血管有明显扩张作用。

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