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• 综述 •

水凝胶弹簧圈治疗急性期颅内破裂动脉瘤的研究现状

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[摘要] 血管内治疗是颅内破裂动脉瘤的重要治疗手段, 然而较高的动脉瘤复发率和早期再出血率使其具有一定局限性。水凝胶弹簧圈是在传统的裸铂金弹簧圈的基础上进行水凝胶涂层修饰形成, 可提高动脉瘤栓塞密度。多项随机对照试验证实水凝胶弹簧圈相较于裸铂金弹簧圈可降低动脉瘤复发率, 但这些研究均基于所有状态的动脉瘤(包括破裂动脉瘤和未破裂动脉瘤), 因此水凝胶弹簧圈是否可降低破裂动脉瘤复发率及早期再出血率目前尚无明确结论。本文对水凝胶弹簧圈治疗急性期颅内破裂动脉瘤的研究现状进行综述。

[关键词] 颅内动脉瘤; 破裂; 水凝胶弹簧圈; 动脉瘤复发; 再出血

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Hydrogel coils in treatment of acute ruptured intracranial aneurysm: research status

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[Abstract] Endovascular treatment with platinum coils has become a vital therapeutic option for ruptured intracranial aneurysms. However, the high aneurysm recurrence rates and early rebleeding cause some limitations. Hydrogel coil, which is consisted of a bare platinum coil and an inner core of hydrogel, is initially designed to improve the packing density of intracranial aneurysm. Several randomized controlled trials have demonstrated that hydrogel coils could significantly reduce the incidence of aneurysm recurrence compared with bare platinum coils. However, the inspiring conclusion was derived from those studies that included all states of intracranial aneurysms (ruptured and unruptured aneurysms). Whether hydrogel coils can reduce the recurrence and early rebleeding of ruptured intracranial aneurysms is still unclear. Therefore, this paper reviews the current status of research on hydrogel coils in the treatment of acute ruptured intracranial aneurysms.

[Key words] intracranial aneurysms; rupture; hydrogel coils; aneurysm recurrence; rebleeding

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颅内动脉瘤是由于先天性脑血管发育异常或后天高血压等多种损伤因素造成的局部脑血管壁异常膨出, 该疾病在世界范围内的发病率为1%~3%^[1-2], 中国人群发病率为7.0%~8.8%^[3-4]。蛛网膜下腔出血的发生率占脑卒中的5%, 而颅内动脉瘤破裂是造成蛛网膜下腔出血最主要的原因, 占80%~85%^[1-2]。在发生动脉瘤性蛛网膜下腔出血(aneurysmal subarachnoid hemorrhage, aSAH)的患者中, 10%~15%因病情过重而在入院前死亡, 27%~44%在入院后死亡^[5], 约1/3在发病

1周内死亡^[2]; 8%~23%的aSAH患者在72 h内会发生再出血^[6-7], 而再出血者死亡率高达62%~73%^[8-9], 因此aSAH的早期积极治疗至关重要。

自Guglielmi等^[10]在1991年首次使用裸铂金弹簧圈(bare platinum coil, BPC)治疗颅内动脉瘤以来, 血管内治疗以其微创、快速的优势迅速成为颅内动脉瘤的重要补充手段。随后的国际蛛网膜下腔出血动脉瘤试验(International Subarachnoid Aneurysm Trial, ISAT)结果表明, 血管内治疗与传统的开颅夹闭相比能够显著降低死亡率, 改善

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临床预后,血管内治疗逐渐成为颅内破裂动脉瘤(ruptured intracranial aneurysm, RIA)的首选治疗手段^[11-14]。然而,系统评价结果显示,使用BPC进行血管内治疗RIA的复发率高达20.1%^[15],年再出血率达0.6%^[16]。这主要是因为BPC的平均堵塞率仅为20%~30%,依靠血栓形成来填充动脉瘤,一部分不稳定的血栓在机化前溶解,从而导致弹簧圈压缩和动脉瘤复发^[17]。而研究证实,栓塞密度与动脉瘤复发、再出血呈负相关^[18-19],因此需要不断改进血管内栓塞材料及栓塞策略以提高动脉瘤堵塞率,从而降低动脉瘤复发率及再出血率,而水凝胶弹簧圈正是基于这个理念而设计的。

1 水凝胶弹簧圈的优势

水凝胶弹簧圈又称Hydrogel弹簧圈,是水凝胶和铂金的混合物,是在传统的BPC基础上进行水凝胶聚合物涂层修饰形成。水凝胶聚合物在接触血液后体积会膨胀(3 min内达到最大体积的80%,并在20 min内达到最大体积),弹簧圈体积增大产生机械占位效应,从而增加动脉瘤的堵塞率、降低动脉瘤复发率^[20]。目前水凝胶弹簧圈有2代产品,第一代水凝胶弹簧圈(HydroCoil)由于硬度大及受操作时间限制,在临床上已基本被第二代水凝胶弹簧圈(Hydrosoft、HydroFrame、HydroFill等)取代。水凝胶弹簧圈相较于传统弹簧圈具有独特的优势:(1)水凝胶弹簧圈采用实芯设计,而非BPC的空芯设计,通过体积膨胀的方式提供更加坚固的机械占位效应,与血栓相比,不易被压缩,对血流阻挡作用更强,从而降低复发率^[21]。

(2)新一代水凝胶弹簧圈采用内芯膨胀设计,具有水凝胶内芯及抗拉伸纤维丝,相较第一代水凝胶弹簧圈(HydroCoil)更柔软,更适合RIA。此外,水凝胶内芯水合作用后膨胀较HydroCoil慢且只会膨胀到一定大小,不会超出铂金圈丝的一级螺旋外径;并且水凝胶内芯膨胀后不会对相邻弹簧圈及动脉瘤壁造成挤压,只会向有空隙的地方膨胀,不会出现过度膨胀而导致动脉瘤破裂的情况^[17]。

(3)惰性的水凝胶不会溶解,可在瘤颈处为血管内皮组织的增生提供稳定、永久的机械平台,通过瘤颈的生物愈合降低复发率^[22]。利用兔动脉瘤模型的组织学研究发现,在BPC和生物活性弹簧圈上没有观察到新生内膜层,而在水凝胶弹簧圈环上

存在新生内皮细胞,表明水凝胶弹簧圈可为内皮细胞提供生长平台,使内皮细胞桥接动脉瘤颈并重建血管壁^[23]。而在大鼠颈外动脉侧壁动脉瘤模型中,与BPC相比,水凝胶弹簧圈引起了更多的组织反应和机化,动脉瘤复发率降低了8.6%^[24]。

(4)水凝胶弹簧圈引起的异物炎症反应低于BPC,有利于组织生长^[25]。(5)水凝胶弹簧圈的圈丝直径、一级和二级螺旋直径是变化的,能匹配膨胀内芯的张力,因此其柔软度范围较大,可用于成篮、填圈和收尾,在不同类型、不同大小的动脉瘤中都可以很好地组合应用^[26]。

2 水凝胶弹簧圈在RIA中的临床应用

未破裂颅内动脉瘤(unruptured intracranial aneurysm, UIA)和RIA血管内治疗的安全性和有效性差别很大,RIA的致残率和死亡率均显著高于UIA,且RIA相较UIA更易发生动脉瘤复发^[27],而目前关于水凝胶弹簧圈治疗的随机对照试验(randomized controlled trial, RCT)及前瞻性队列研究中,绝大多数的研究对象是所有状态的动脉瘤(既有UIA也有RIA)或仅为UIA,很少单独对RIA进行安全性和有效性评价,因此目前针对所有状态动脉瘤的研究得出的水凝胶弹簧圈优于BPC的结论尚需谨慎对待。只有将现有研究中的关于RIA数据进行二次分析,才能更好地评价水凝胶弹簧圈治疗RIA的安全性和有效性,也才能更准确地定义水凝胶弹簧圈的特定适应证。

2.1 水凝胶弹簧圈治疗RIA的安全性 RIA早期再出血往往导致预后不良甚至死亡,因此也被认为是最严重的并发症^[8-9]。由于动脉瘤早期再出血主要发生在首次aSAH后的72 h内^[6],因此2012年美国心脏协会/美国卒中协会指南建议应尽早对RIA进行治疗^[28]。2017年一项meta分析显示,与晚期(aSAH 24 h后)血管内治疗相比,早期(aSAH 24 h内)血管内治疗可改善RIA患者的临床结局,然而与aSAH后24~72 h治疗相比未发现临床获益^[29]。另一项回顾性研究甚至表明,与aSAH后24~72 h治疗相比,SAH后24 h内早期治疗会使RIA患者受到伤害^[30]。此外,van Lieshout等^[31]报道了471例RIA血管内治疗病例资料,发现与aSAH后6~72 h血管内治疗相比,aSAH后6 h内血管内治疗与治疗相关的动脉瘤再破裂风险

增加和结局不良相关。因此目前尚无法通过在治疗时机上做出改变以改善 RIA 患者的临床预后,而水凝胶弹簧圈从栓塞材料角度为我们提供了可能进一步降低 RIA 早期再出血率的重要突破口。

2011 年一项 RCT 研究 (HELPS) 对比了 HydroCoil 和 BPC 治疗颅内动脉瘤 (包括 UIA 和 RIA) 的安全性和有效性,该研究 HydroCoil 组纳入了 132 例 RIA 患者, BPC 组纳入了 117 例 RIA 患者,采用复合结局 (影像学复发和临床预后不良) 评价治疗效果,未提及 RIA 亚组的围手术期并发症发生情况,18 个月随访结果显示两组的临床良好预后率相当,而 HydroCoil 组复合结局显著优于 BPC 组 (68% vs 50%, $OR=2.08$, 95% $CI: 1.24\sim 3.46$, $P=0.014$)^[32]。Brinjikji 等^[33]对 HELPS 研究中大小 (5~9.9 mm) 的 RIA 单独进行分析,15~18 个月临床随访结果表明 HydroCoil 组和 BPC 组良好预后率的差异依然无统计学意义 (88.3% vs 89.9%, $P=0.69$)。2018 年一项 RCT 研究 (GREAT) 对比了新一代水凝胶弹簧圈和 BPC 治疗颅内动脉瘤的安全性和有效性,该研究水凝胶弹簧圈组和 BPC 组分别纳入了 103 例和 105 例 RIA 患者,18 个月随访显示两组良好预后率相当 (89.6% vs 91.1%),而水凝胶弹簧圈组不良复合终点率低于 BPC 组 (28.7% vs 38.6%),但差异无统计学意义 ($P=0.19$),经过校正基线资料后发现水凝胶弹簧圈组不良复合终点率较 BPC 组降低 8.4% ($P=0.036$)^[34]。

Dabus 等^[35]开展了一项第二代水凝胶弹簧圈治疗 RIA 的多中心回顾性单臂研究,围手术期总并发症发生率为 3.75% (3/80),3 例均为术中动脉瘤破裂,无动脉瘤再出血发生,临床良好预后率为 76.3%。此外,多项研究显示将水凝胶弹簧圈置于瘤颈处能增加动脉瘤远期闭塞率及降低动脉瘤复发率^[36-37]。而 Brinjikji 等^[38]开展的一项前瞻性单盲多中心注册研究 (GEL THE NEC) 主要评价了 HydroSoft 作为最后的弹簧圈放置在瘤颈处的安全性和有效性,该研究纳入 3~15 mm 的动脉瘤 599 例,其中 RIA 214 例,技术成功率达 96%,操作相关并发症发生率为 9.8%,操作相关致残率为 1.4%,操作相关死亡率为 0,无早期再出血发生。Waldau 等^[39]开展了 61 例 HydroSoft 治疗 RIA 的多中心回顾性研究,围手术期血栓形成 3 例 (4.9%),

术中破裂 2 例 (3.3%),术后再出血 1 例 (1.6%)。HEAL 研究报道 HydroCoil 术中动脉瘤破裂率为 2.8%^[40],而 BPC 术中动脉瘤破裂率高达 4.1%^[41]。

国内学者对水凝胶弹簧圈的安全性和有效性也进行了相当多的报道,但绝大多数为单中心、回顾性、小样本系列的非对照研究,且多数包括 UIA 和 RIA,少有专门针对 RIA 的对照研究。Ya 等^[42]报道了 31 例使用 HydroCoil 治疗急性期 RIA 单中心病例系列,术中无并发症发生,无临床随访和影像学随访。Guo 等^[37]比较了 HydroSoft 与 HydroCoil 的治疗效果,发现 HydroCoil 组术中破裂率高达 5.0% (3/60),而 HydroSoft 组无术中破裂发生,这可能是由于 HydroCoil 较硬所致。Jiang 等^[43]比较了 HydroSoft 与 BPC 治疗急性 RIA 的安全性,发现两组围手术期并发症发生率差异无统计学意义。

2.2 水凝胶弹簧圈治疗 RIA 的有效性 与外科开颅夹闭不同的是,血管内治疗往往需要一段时间进行动脉瘤修复,主要是内皮细胞生长和血栓形成。多项临床研究显示,对于 RIA,不充分的栓塞往往与较高的复发率和再出血率相关^[18,44-46]。一项 RCT 研究 (GREAT) 结果显示水凝胶弹簧圈平均动脉瘤填塞率高于 BPC (39% vs 31%, $P<0.001$),且水凝胶弹簧圈可以用更少的弹簧圈获得更高的填塞密度^[47];另一项纳入 622 例患者的多中心回顾性队列研究也显示 HydroSoft 组的平均动脉瘤填塞密度显著高于 BPC 组 [(36.0±8.50)% vs (32.1±8.22)%], $P<0.001$ ^[21],但以上结果均基于 UIA 和 RIA。国内 Jiang 等^[43]针对 RIA 比较了 HydroSoft 与 BPC 的有效性,结果显示 HydroSoft 组较 BPC 组具有更高的动脉瘤填塞率 (44.5% vs 29.8%, $P=0.014$),影像学随访 (HydroSoft 组平均随访时间为 9.3 个月, BPC 组为 10.1 个月) 显示 HydroSoft 组也具有更高的动脉瘤完全闭塞率 (89.1% vs 70.6%, $P=0.043$)。

关于水凝胶弹簧圈的单臂研究影像学随访结果显示 RIA 完全闭塞率为 63.5%~77.8%,复发率为 6.4%~18.2%,再治疗率为 3%~7.4%^[35,37-38,48]。Khan 等^[49]比较了 Matrix、BPC 和水凝胶弹簧圈治疗 RIA 的有效性,6 个月影像学随访结果显示水凝胶弹簧圈组动脉瘤完全闭塞率为 60.0%,显著高于 BPC 组的 25.0% ($P=0.01$)。HELPS 和 GREAT 两项 RCT 研究的 RIA 亚组分析均表明,水凝胶弹

簧圈组与BPC组临床良好预后率相当,但水凝胶弹簧圈组不良复合终点率较BPC组显著降低,且差异均有统计学意义($P=0.014$ 、 0.036)^[32,47]。Brinjikji等^[33]进一步对HELPS研究中的288例中等大小(5~9.9 mm)动脉瘤单独进行了随访研究,其中RIA 149例(水凝胶弹簧圈组和BPC组分别74例和75例),影像学随访表明对于RIA患者,3~6个月、15~18个月水凝胶弹簧圈组的重大复发率均显著低于BPC组(7.1% vs 26.0%, $P=0.02$; 20.3% vs 47.5%, $P=0.003$);而对于UIA患者,两组重大复发率相当(16.7% vs 14.8%, $P=0.80$)。此外,对RIA进行多因素分析结果显示,水凝胶弹簧圈组重大复发率较低($OR=0.27$; 95% CI : 0.12~0.58, $P=0.0007$)。一项meta分析显示,对于RIA占比超过30%的研究而言,水凝胶弹簧圈组较BPC组具有更高的动脉瘤闭塞率($RR=1.21$, 95% CI : 1.07~1.38, $P=0.002$);而对于RIA占比小于30%的研究,水凝胶弹簧圈组与BPC组影像学结果差异无统计学意义^[50]。以上结果提示水凝胶弹簧圈对于RIA的影像学获益似乎大于UIA。

3 小结

水凝胶弹簧圈相较于传统的BPC具有独特的优势,能通过体积膨胀的方式提供更坚固的机械占位效应,对血流阻挡作用更强,可增加RIA即刻栓塞密度及降低远期复发率。虽然水凝胶弹簧圈治疗RIA的再出血率较低,但与BPC相比其是否可降低再出血率尚不明确,仍需要进一步临床研究数据支持。

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