秋水仙碱在冠状动脉粥样硬化性心脏病防治中的研究进展与争议

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【摘要】既往大量研究表明炎症在冠状动脉粥样硬化性心脏病(冠心病)的发生和发展中扮演了重要角色,抗炎治疗一直是冠心病研究领域的热点。近年几项大型临床研究发现秋水仙碱可预防冠心病患者不良心血管事件的发生,改善冠心病患者的预后,但同时秋水仙碱在临床应用中也存在诸多争议。现就秋水仙碱在冠心病防治中的最新研究进展及存在的争议做一综述。

【关键词】炎症;冠状动脉粥样硬化性心脏病;秋水仙碱
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Research Progress and Controversy of Colchicine in Prevention and Treatment of Coronary Atherosclerotic Heart Disease

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【**Abstract**】A large number of previous studies have shown that inflammation plays an important role in the occurrence and development of coronary atherosclerotic heart disease(CHD), and anti-inflammatory therapy has always been a hot spot in the field of CHD. In recent years, several large-scale clinical studies have found that colchicine can prevent adverse cardiovascular events in patients with CHD and improve the prognosis of patients with CHD. However, there are also many controversies in the clinical application of colchicine. This article reviews the latest research progress and existing controversies of colchicine in the prevention and treatment of CHD.

【**Key words**】Inflammation; Coronary atherosclerotic heart disease; Colchicine

冠状动脉粥样硬化性心脏病(冠心病)是临床上常见的慢性疾病,大量研究已证实炎症与冠心病密切相关。但抗炎药物的研发举步维艰,至今无一款能明确适用于冠心病患者的抗炎药物问世。近期研究表明秋水仙碱可通过独特的抗炎途径降低冠心病患者不良心血管事件的发生率,因此,有必要对秋水仙碱在冠心病中的作用机制做进一步探讨。

1　抗炎药物的研究进展

既往的研究表明炎症参与了冠心病的发生、发展及预后[1],抗炎治疗逐渐成为冠心病防治的新靶点。非甾体类抗炎药增加心肌梗死的风险[2],而皮质类固醇被发现无效甚至增加心脏破裂的风险[3]。甲氨蝶呤不仅不能降低冠心病患者的心血管事件风险,还会导致感染等风险增加[4],作为新药的白介素(IL)-1β单克隆抗体 canakinumab 虽然被证明能降低心肌梗死后心血管事件的发生率,但其高昂的价格和可能导致感染增加的特点限制了其广泛应用[5]。MCC950,一种富含亮氨酸重复序列和含吡咯结构域 3 的核苷酸结合结构域(NLRP3 炎性小体)抑制剂,在动物实验中被证明可减少心肌梗死面积并保护心脏功能[6],但尚未在人群中开展试验,此外,他汀类药物也被发现有一定的抗炎作用[7],但机制尚不清楚。由此可见,上述药物目前都无法用于冠心病的抗炎治疗,而秋水仙碱价格低廉,副作用少,临床应用经验丰富,患者耐受性好,是目前最有希望应用于冠心病的抗炎药物。

2　秋水仙碱的作用机制

秋水仙碱主要通过以下几个方面发挥作用:(1)通过与中性粒细胞的微管蛋白结合来影响细胞膜的功能,从而抑制中性粒细胞的趋化、黏附、吞噬和变性能力,在慢性冠状动脉疾病患者中可观察到中性粒细胞活性被秋水仙碱抑制[8];(2)抑制 L 选择素在中性粒细胞的表达,损害了中性粒细胞的迁移能力;(3)抑制 E 选择素在内皮的表达,减少炎症细胞对内皮的黏附;(4)抑制磷脂酶 A2,减少单核细胞和中性粒细胞释放

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前列腺素和白三烯;(5)NLRP3 炎性小体可促进 IL-1β 和 IL-18 的成熟和分泌,秋水仙碱可从四个方面阻断 NLRP3 炎性小体的活性[9]:①抑制 MEFV 基因的表达,阻止 NLRP3 炎性小体的合成;②通过与微管蛋白结合抑制炎性小体的功能共定位;③直接阻断胱天蛋白酶-1 的表达;④抑制 P2X7 介导的孔隙形成,影响 NLRP3 炎性小体的激活;(6)通过与血小板微管蛋白结合影响血小板的活化和聚集,秋水仙碱对体内外纯血小板聚集无影响,而对中性粒细胞-血小板和单核细胞-血小板聚集产生影响[10]。此外,秋水仙碱还可能通过降低微小核糖核酸水平,减轻急性冠状动脉综合征(acute coronary syndrome, ACS)的炎症反应[11]。

其中,秋水仙碱通过 NLRP3 炎性小体发挥抗炎作用仍有争议,有学者发现 NLRP3 蛋白可能在急性心肌梗死中不起作用,因为其在心脏的表达水平较低[12],另一方面,也有学者提出秋水仙碱不一定能激活 NLRP3 炎性小体[13]。因此,秋水仙碱的作用机制值得进一步研究,为今后的大型临床研究提供基础证据。

3 秋水仙碱在冠心病中的临床研究

3.1 秋水仙碱与慢性冠状动脉疾病

既往针对痛风患者的研究表明,与不服用秋水仙碱的患者相比,服用秋水仙碱的痛风患者的心肌梗死发生率明显降低[14]。这似乎从侧面表明秋水仙碱治疗冠心病的潜力。Fiolet 等[15]观察到秋水仙碱降低了慢性冠状动脉疾病患者的 IL-6(从 2.51 ng/L 降至 2.22 ng/L, $P=0.04$))和超敏 C 反应蛋白(hs-CRP)(从 4.40 mg/L 降至 2.33 mg/L, $P<0.01$)水平。一项纳入 64 例接受了阿司匹林和他汀类药物治疗且 hs-CRP > 2 mg/L 的稳定性冠心病患者的试验表明,服用秋水仙碱(0.5 mg/次,2 次/d)在 4 周内显著降低了 hs-CRP 水平[基线 hs-CRP 水平从(4.58 ± 2.05)mg/L 降至(1.78 ± 1.38)mg/L, $P<0.001$][16]。随之而来的 LoDoCo 试验证明小剂量秋水仙碱(0.5 mg/d)对稳定性冠心病的二级预防安全且有效[17]。进一步的 LoDoCo2 研究结果显示:与安慰剂组相比,秋水仙碱组(0.5 mg/d)的心血管风险降低 31%(*HR* = 0.69, 95% *CI* 0.57 ~ 0.83, $P<0.05$)[18]。近期的荟萃分析也表明,秋水仙碱降低了冠心病患者不良心血管事件的风险[19-20]。

3.2 秋水仙碱与 ACS

有证据表明,在 ACS 的早期阶段,炎症加剧,不良心血管事件的风险增加[21]。Vaidya 等[22]发现秋水仙碱可稳定 ACS 患者动脉粥样硬化斑块。Deftereos 等[23]提出在心肌梗死发生后的短时间内使用秋水仙碱可减少心肌梗死面积。COLCOT 试验证实小剂量秋水仙碱(0.5 mg/d)可显著降低心肌梗死患者 30 d 内的缺血性心血管事件风险(*HR* = 0.77, 95% *CI* 0.61 ~ 0.96, $P=0.02$)[24]。除了在心肌梗死后的早期阶段减少心肌梗死面积,秋水仙碱还对心脏血流动力学产生长期和潜在的积极作用。研究表明,在急性心肌梗死后应用秋水仙碱,8 周后超声心动图显示心输出量增加[25]。此外,在左前降支冠状动脉永久闭塞后,秋水仙碱改善了心肌梗死恢复期的不良心室重塑,抑制了心力衰竭的发展[26]。秋水仙碱还可能具有改善 ACS 患者血管内皮功能的作用[27]。

3.3 秋水仙碱与经皮冠状动脉介入治疗

研究发现经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)后的残余炎症风险与主要不良心血管事件风险增加相关(*HR* = 2.10, 95% *CI* 1.45 ~ 3.02, $P<0.001$)[28]。Martínez 等[29]证明,在心导管插入术前口服秋水仙碱可显著抑制 ACS 患者局部心脏炎症细胞因子(IL-1β、IL-18 和 IL-6)的产生。Shah 等[30]将 400 例接受 PCI 的患者随机分配到 1.8 mg 秋水仙碱组(PCI 前 1 ~ 2 h 1.2 mg, 1 h 后 0.6 mg)或安慰剂组。结果显示秋水仙碱治疗降低了 hs-CRP 和 IL-6 水平,但并未降低 PCI 相关心肌损伤的风险。PCI 后炎症生物标志物升高与支架内再狭窄风险增加相关。由于秋水仙碱具有抗炎特性,它可能具有预防 PCI 后再狭窄的作用。虽然 1992 年发表的研究首次发现秋水仙碱不能降低 PCI 后再狭窄的发生风险[31],但 2013 年的一项研究表明秋水仙碱可降低糖尿病患者的支架内再狭窄率($P=0.002$)[32]。因此,秋水仙碱是否能影响 PCI 患者的预后还需进一步探讨。

4 争议与展望

尽管诸多研究表明秋水仙碱在冠心病的防治中有广阔的应用前景,但现今的临床应用中仍存在不少争议,值得临床工作者谨慎对待。

4.1 安全性

COPS 试验表明秋水仙碱组的总死亡率(8 vs 1, $P=0.017$)与非心血管疾病死亡率(5 vs 0, $P=0.024$)均高于安慰剂组[33],但其样本量较小,需进行更大样本量的研究后继续探讨是否存在因果关系。最近的一项 meta 分析显示,秋水仙碱会增加腹泻和胃肠道不良事件的发生率,但不会增加感染的发生率[34]。此外,秋水仙碱还可能由于其潜在的抗血小板作用而增加出血的风险[35]。在接受秋水仙碱长期治疗的家族性地中海热患者中,秋水仙碱引起的可逆的白细胞减少症发生率为 10.8%[36]。因此,建议对长期接受秋水仙碱治疗的患者进行血细胞计数和凝血功能的监测。

4.2 药物相互作用

除不良反应外，另一个阻碍秋水仙碱广泛应用的因素可能是潜在的药物间相互作用，其中被广泛报道的是秋水仙碱与他汀类药物间的相互作用。Baker 等[37]观察到同时使用他汀类药物和秋水仙碱的患者横纹肌溶解的风险增加，但也有研究者发现秋水仙碱与他汀类药物联合使用在短期内具有协同降脂作用[38]，所以，药物间相互作用并不总是有害的。此外，秋水仙碱与钙通道阻滞剂和替格瑞洛等合用时会增加血药浓度，进而增加不良反应发生率。因此，为避免此类现象的发生，建议秋水仙碱与这类药物合用时监测肌酸激酶，并适时调整药物剂量。

4.3 有效性

在秋水仙碱有效性问题上也有不一致的观点。有研究显示秋水仙碱不能降低心肌梗死后 C 反应蛋白水平[39]。2020 年公布的 COPS 临床试验的结果显示，在标准药物治疗中加入秋水仙碱不会显著影响 ACS 患者 12 个月时的心血管结局（$P=0.09$），并且与较高的死亡率相关（$P=0.017$）[33]。Hemkens 等[40]提出秋水仙碱对冠心病患者全因死亡率无影响。McKnight 等[41]认为如果秋水仙碱在 PCI 后给药超过 30 d，可能会减少 ACS 患者的主要不良心血管事件，而如果仅在 PCI 前给药，则似乎无效。由于目前已发表的研究随访时间不长，入组人数有限，以后还需进行更多的大型临床研究来证明其有效性。

4.4 展望

从目前的研究结果来看，秋水仙碱有极大的潜力成为冠心病防治的新基石，但现有研究仍有不足：（1）目前的研究未探讨秋水仙碱不同剂量之间的差异性；（2）未划分年龄组来探讨其最佳适用人群；（3）秋水仙碱在冠心病一级预防中的适用性也值得进一步研究。此外，国内也可开展相关研究来排除种族差异。总的来说，秋水仙碱在冠心病中的研究仍处于初步阶段，未来仍需包含更大样本量及更长随访时间的大型研究去探索秋水仙碱在冠心病中的临床应用价值，从而为冠心病的防治提供新疗法。

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(上接第 25 页)

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