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围手术期阿司匹林使用与血小板功能检测的研究进展

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[摘要] 血小板在生理性止血以及病理性动脉血栓形成中起关键作用。阿司匹林因具有良好的抗血小板作用已成为心血管疾病人群的主要治疗方式, 特别是心血管介入治疗术后且有外科手术需求的患者。针对此类患者, 外科医生面临复杂凝血问题, 即在围手术期使用阿司匹林抗凝的同时, 也存在术中增加出血量的风险。然而, 目前缺乏围手术期阿司匹林规范使用的指南, 且在血小板功能检测方面没有标准化。

[关键词] 阿司匹林; 围手术期; 血小板弹力图

Research advances in aspirin management during perioperative period and clinical examination of platelet function

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Abstract Platelet mainly contributes in physical hemostasis and pathological thrombosis. The fundamental antiplatelet drug, aspirin, is widely used for primary prevention of cardiovascular disease (CVD), especially patients received percutaneous coronary intervention (PCI). The antiplatelet therapy in perioperative period for patients with established PCI is quite complex, as the effective antiplatelet dosage might, on the other hand, increases the risk of bleeding during the surgery. Unfortunately, there is no specific, widely-accepted recommendation for these situation. What's worse, the standard for the perioperative platelet function indicators is vacant.

Keywords aspirin; perioperative; thromboelastography

随着我国人口老龄化的加剧, 心血管疾病等的患病率持续上升, 长期服用低剂量阿司匹林的人群越来越大。心血管病患者在外科手术之前是

否停用阿司匹林, 并没有统一的指南。本综述主要探讨各类手术围手术期是否停用阿司匹林的研究进展。

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1 阿司匹林抗血小板机制

阿司匹林是人类医药史上三大经典药物之一。一方面,阿司匹林具有解热镇痛的作用,被用于治疗发热、疼痛及类风湿关节炎等疾病;另一方面,阿司匹林是环氧酶(cyclo-oxygenase, COX)的抑制剂^[1],具有抗血小板聚集的功能。机体内COX是花生四烯酸(arachidonic acid, AA)生成前列腺素H₂和血栓烷A₂(thromboxane A₂, TXA₂)的关键酶,主要有COX-1和COX-2两种形式。血小板中,COX-1调节前列腺素H₂的产生,后者在血栓烷合成酶的诱导下生成TXA₂。血栓烷负责激活新的血小板,刺激血小板聚集和血管收缩,从而促进血栓形成。阿司匹林通过调控AA/TXA₂这一途径发挥抗血小板的作用^[2]。作为一种不可逆血小板酶环氧合酶抑制剂,临床上广泛用于心脑血管疾病一级和二级的预防。美国有超过5 000万成年人服用阿司匹林以用于心血管疾病的一级或二级预防^[1]。

2 围手术期使用阿司匹林的争议

因具有良好的抗血小板聚集作用,阿司匹林被多项指南推荐为心血管疾病的二级预防并终生服用^[3-4]。非致死性心肌梗死患者服用阿司匹林后,病死率显著下降^[5]。相反,长期服用阿司匹林人群没有大手术或出血的情况下停用,心血管事件发生率增加30%^[6],而围手术期停用阿司匹林导致主要不良心血管事件的概率增加了3倍^[7]。尽管阿司匹林停药导致的血栓风险在围手术期会加剧,但为了防止术中出血过多,目前国内大部分外科手术均要求手术前停用阿司匹林5~7 d——因为血小板寿命是7~14 d,每天约更新血小板总量的1/10,停用阿司匹林5~7 d,即恢复达到总量的50%,血小板功能基本恢复到正常水平。

围手术期是否继续或停止使用阿司匹林,已经成为一个重要的医学问题。而选择的关键取决于围手术期出血风险与血栓栓塞事件的风险。患者服用的药物及手术的类型等因素都会导致不同的出血风险、血栓风险,因此术前该不该停阿司匹林不能一概而论,应该针对不同情况具体讨论。大部分手术围手术期使用阿司匹林不仅不会增加出血风险,而且还能有效防控心血管事件的发生^[7]。

3 各类手术围手术期阿司匹林使用规范

3.1 神经外科手术

阿司匹林是颅内手术术后发生血肿的重要危险因素^[8]。国外专家坚持在术前停用阿司匹林,这样可以优化围手术期凝血状态以降低术后出血并发症的风险^[9]。在我国,考虑术后颅内出血可能导致颅内血肿等严重并发症,目前也主张围手术期停用阿司匹林。2018年发表在《中华医学杂志》上的《神经外科围手术期出血防治的专家共识(2018)》^[10]建议对于择期神经外科手术患者,术前应停用阿司匹林5~10 d。

需要指出的是,在神经外科领域新近一些研究提出围手术期阿司匹林不影响术后风险。如,Rahman等^[11]评估了2010至2014年接受手术切除脑肿瘤患者病历,分析显示围手术期使用低剂量阿司匹林与围手术期出血风险无关。在>65岁的老年创伤性颅脑外伤患者中,口服低剂量阿司匹林并未增加术后出血的风险,与住院时间长短和院内病死率无关^[12]。同时,Kamenova等^[13]也发现在脑室腹腔分流术中,在围手术期阿司匹林使用者和非使用者的术后出血事件无统计学意义。这些证据都表明神经外科手术过程中继续使用阿司匹林不会增加出血风险。然而上述文献病例数都有限,不足以作为围手术期继续使用阿司匹林提供依据。因此在更多神经外科相关手术围手术期使用阿司匹林的安全性的研究结果发布之前,目前对于神经外科手术患者,术前应停用阿司匹林。

3.2 眼科手术

眼科手术围手术期使用阿司匹林可能引起视力受损甚至致盲,因此,目前国内大多数眼科手术术前均要求停用阿司匹林。国外一项调查^[14]显示:82.7%的医生会在青光眼手术前常规中断阿司匹林。

然而,越来越多的研究证实部分眼科手术围手术期使用阿司匹林并未增加出血风险。低剂量阿司匹林对于白内障围手术期出血和出血风险没有影响,还会减少心血管事件的发生^[15-16]。2010年英国皇家眼科医学院基于一项多中心、大样本研究结果,修订了其白内障手术指南,建议在白内障手术前不需要停用阿司匹林等抗血小板药物^[17]。

那么,眼科围手术期阿司匹林应该如何使用?

基于目前的文献证据, 权衡出血风险和血栓风险后, 推荐一些低出血风险手术——玻璃体注射、白内障手术^[18]、斜视手术、角膜手术、玻璃体视网膜手术^[19-20]、青光眼手术(小梁切除术)^[21]——期间继续使用阿司匹林, 而在一些高出血风险手术^[22], 如青光眼手术(非小梁切除术)、眼眶手术、隔后眼睑手术仍应坚持停用阿司匹林。

3.3 骨科手术

深静脉血栓形成与肺栓塞是骨科手术的常见并发症, 在没有药物预防的情况下, 发生率高达60%^[23], 可导致患者死亡。目前, 在美国阿司匹林已成为预防深静脉血栓主要方式^[24-25], 且疗效很好^[26-27], 因此在骨科手术中, 服用阿司匹林的收益远远大于出血风险。阿司匹林广泛应用于骨科大手术中以预防血栓, 不仅因其预防血栓效果极佳, 且不需要常规的血液检测, 大量临床试验^[28-32]证明了其在关节成形术及髌部骨折术中预防血栓的有效性和安全性。美国骨科医师学会^[33]及美国胸科医师协会^[34]均推荐, 对于骨科大手术, 尤其是围手术期深静脉血栓风险高的手术如髌部骨折术(hip fracture surgery, HFX)、全髌关节置换术(total hip replacement, THR)、全膝关置换术(total knee replacement, TKR)等, 应使用阿司匹林作为预防血栓措施之一。

除关节成形术及髌部骨折术的骨科手术外, 其他类型的骨科手术围手术期是否也应继续使用阿司匹林呢? 一项前瞻性病例对照研究结果^[35]显示: 股骨近端骨折中围手术期继续服用阿司匹林与病死率、大出血、输血要求及术后引流并不相关, 低剂量阿司匹林在股骨近端骨折患者中是安全的。其次, Edmunds等^[36]研究结果显示: 在手术中, 单一服用阿司匹林的患者在术后的出血风险并未增加及血肿等并发症。此外, 在最新POISE-2实验^[37]中, 有大量接受骨科手术的患者, 其中在围手术期接受阿司匹林治疗较对照组没有出现更高的出血风险, 这为我们在骨科围手术期使用阿司匹林提供了权威的证据。目前, 我们认为在骨科(除脊柱外科外)围手术期继续使用阿司匹林是安全且必要的。

3.4 普外科手术

术前停用阿司匹林的目的是减少手术过程中的出血风险及并发症。2013年发表在《中华实用外科杂志》上的《接受抗凝药物治疗的普外科病人围手术期处理——中山共识》^[38]推荐: 一般

情况下, 对于择期手术病人, 如术前服用阿司匹林, 建议停药至少5 d, 最好10 d。目前国内普外科围手术期普遍停用阿司匹林。

然而最近国外很多研究表明普外科围手术期持续服用阿司匹林并未增加出血风险。Wolf等^[39]报道在择期胰腺外科手术中, 如胰十二指肠切除术、远端胰腺切除术和全胰切除术, 整个围手术期继续进行阿司匹林治疗与围手术期出血、输血要求及胰腺手术相关并发症增加无关。Ono等^[40]报道腹腔镜胆囊切除术和结直肠癌切除围手术期继续使用阿司匹林治疗不会增加失血和相关并发症。一项随机对照试验^[41]结果也显示: 在择期胆囊切除术、腹股沟疝修补术及结直肠外科手术的整个围手术期, 低剂量阿司匹林是安全的。

基于最新研究进展, 中华医学会外科分会于2016制定的《中国普通外科围手术期血栓预防与管理指南》^[42]提出: 1)对于出血风险低的小手术, 可以不停用抗血小板药物; 2)对服用阿司匹林单药的患者: 如心血管事件程度为中至高危, 可不停药, 但需注意出血风险。

鉴于腹部手术术式的多样性, 针对不同的手术类型有不同的出血风险, 规范使用阿司匹林不能一概而论。目前, 迫切需要大型随机对照试验, 为全身或者腹部各手术中阿司匹林的处理提供准确的循证依据, 更好地服务于临床。

3.5 心外科手术

虽然在冠状动脉搭桥术前使用阿司匹林与围手术期出血风险增加相关^[43-44], 但这种风险可以降低, 甚至消除, 在冠状动脉旁路手术前使用阿司匹林是安全的^[45-46]。而且, 近年来发现冠状动脉搭桥手术前低剂量阿司匹林显著降低围术期心肌梗死的发生率^[47-48]。在心脏外科、冠状动脉旁路移植术中使用阿司匹林的益处已得到充分证实^[49-50]。

围手术期使用阿司匹林不仅可以改善冠状动脉搭桥术患者的结局, 对其他心脏手术的患者也有益处^[48-49]。Cao等^[47]报道在心脏手术术前阿司匹林治疗显著降低重大心脑血管并发症、肾衰竭、重症监护病房停留和30 d病死率的风险, 但不会增加心脏手术患者再次住院的风险。

基于这些临床证据, 2011年美国心脏病学基金会、美国心脏协会及美国胸科医师协会均推荐, 对于将进行冠状动脉搭桥术患者, 不应中断阿司匹林的治疗^[51]。欧洲心脏病学会和欧洲心胸外科协会均建议在心胸外科术前不应停用阿司匹林^[52]。

3.6 泌尿外科手术

最近由美国泌尿学协会和国际泌尿外科疾病咨询委员会共同组成的多学科小组(包括泌尿科医师, 心脏科医师和血液科医师)制定了关于阿司匹林在泌尿外科围手术期的指南。指南认为, 当阿司匹林作为心血管疾病二级预防时, 所有泌尿外科围手术期在适当注意止血的情况下均可以继续阿司匹林治疗^[53]。与之一致, 最新研究表明高危泌尿手术(部分肾切除术)围手术期使用阿司匹林与出血并发症无相关性且能降低围手术期血栓风险^[54]。

4 血小板功能检测在围手术期的应用

纵观各类手术围手术期阿司匹林的风险与受益, 可见个性化评估出血风险对科学规范化使用阿司匹林具有重要意义。目前在临床上, 应用最多的小血小板定量分析及出血时间, 虽然操作简单且快速, 但与围手术期出血的关联性差, 因此血小板功能检测日益受到关注。

目前, 光学比浊集合度(light transmission aggregometry, LTA)被认为是血小板功能检测的金标准, 能预测心血管患者发生血栓的风险^[55]。然而, LTA在技术上繁琐且耗时长, 在先天性血小板疾病评估之外的围手术期中并未广泛应用^[56]。因此也促进了床旁血小板功能检测(point-of-care testing, POCT)的发展, 常用的方法主要有: VerifyNow仪检测、血栓弹力图(thromboelastography, TEG)、电极阻抗聚集度测定法等。

VerifyNow是一种基于光学比浊法的血小板功能检测方法, 可全自动完成所有检测程序, 分别以阿司匹林反应单位(aspirin reaction units, ARU)或P2Y₁₂反应单位(P2Y₁₂ reaction units, PRU)为检测数值, 可检测阿司匹林或P2Y₁₂拮抗剂的抗血小板疗效。虽然它的术中和术后使用可能受到低血细胞比容的阻碍产生误差, 但其在术前检测结果能很好反应血小板的聚集率, 对术前阿司匹林的使用具有指导作用^[57]。

TEG基于血栓弹力描记检测血小板功能。其中MA值主要反应血小板功能, MA>70 mm, 血小板功能较强, 发生血栓的风险大; MA<50 mm, 血小板功能较弱, 出血风险较大。目前在急诊严重创伤、宫外孕破裂出血消化道大出血等复杂凝血功能障碍的疾病中已经得到广泛应用。Mahla等^[58]研究显示在冠状动脉搭桥手术中采用TEG指导抗凝药物的使用, 并未增加患者术后出血风

险, 减少了患者等待手术时间。

电极阻抗聚集度测定法(multiple electrode aggregometer, MEA)可以检测出血风险, 并被提议作为快速诊断术后出血的工具, 且检测结果与LTA有较好的一致性。其次, 与TEG相比, MEA被证明能更好地预测围手术期出血^[59]。

各种血小板功能检测方法只能从不同的侧面反应部分血小板功能, 在指导围手术期阿司匹林的使用方面尚未达成共识, 还需要更多临床实验证据。随着血小板功能检测手段不断发展, 围手术期阿司匹林的使用必将从手术类型的分类走向个体化治疗, 在预防出血的同时, 降低心血管事件的发生率。

5 结语

目前除一些高出血风险的手术(颅内手术、脊髓手术、眼后房)外, 阿司匹林不必经验性停用, 也不必术前停用5~10 d。因患者对抗血小板治疗反应存在差异性, 在临床工作中, 应该充分考虑个体化治疗, 在血小板功能检测手段的提示下, 由心血管医师、外科医师和麻醉师共同商讨, 确立围手术期阿司匹林规范化使用方案, 真正保障患者围手术期的安全。

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