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阿司匹林、氯吡格雷及西洛他唑预防和治疗老年冠脉支架植入术后血小板高反应性的临床效果观察*

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摘要 目的:探讨阿司匹林、氯吡格雷及西洛他唑预防和治疗老年冠脉支架植入术后血小板高反应性的临床效果。**方法:**选择60例拟行冠脉支架植入术的老年患者,随机地分为加用或未加用200 mg西洛他唑负荷剂量组。术前、术后24小时及术后30天时检测和比较各组患者的血小板聚集功能。**结果:**三联抗血小板治疗组的PRU、ARU及P2Y12 % inhibition值均较两联抗血小板治疗组显著降低,差异具有统计学意义(P<0.05)。三联抗血小板治疗和两联负荷剂量的抗血小板治疗的给药时间(第一次投药至冠脉介入治疗的时间间隔)分别为10.2小时(95%可信区间:7.4-13.1小时)和7.8小时(95%可信区间:4.5-11.2小时),三联抗血小板治疗组术前HPPR (83.3%和46.7%,P=0.003)、术后24小时(36.7%和13.3%,P=0.018)及术后30天HPPR (40.0%和16.7%,P=0.045)的发生率均较两联抗血小板治疗组明显降低(P<0.05)。在术后30天的随访观察期间,两联抗血小板治疗组2例患者出现支架内血栓,并进行了血运重建术;无1例心源性死亡、缺血性卒中及出血性并发症的发生。两组次要终点的发生率比较无显著性差异(P>0.05)。**结论:**在两联抗血小板聚集治疗的基础上附加200 mg西洛他唑可显著降低冠状动脉支架植入术后血小板的高反应性。

关键词:西洛他唑;血小板;药物洗脱支架

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Clinical Research on the Effect of Asprine, Clopidogrel and Cilostazol on the Prevention and Treatment of Elderly Patients Planning for Percutaneous Coronary Intervention*

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ABSTRACT Objective: To investuge the clinical efficacy of asprine, clopidogrel and cilostazol in the prevention and treatment of elderly patients Planning for Percutaneous Coronary Intervention. **Methods:** Sixty elderly patients undergoing coronary intervention were enrolled and randomly treated by 300 mg of aspirin and clopidogrel with or without 200 mg of cilostazol. All loading doses were given at least 3 h before percutaneous coronary intervention and followed by dual or triple maintenance-dose therapy. The platelet function tests were performed just before and at 24 h and 30 days after percutaneous coronary intervention by light transmittance aggregometry and VerifyNow P2Y12 assay. **Results:** The P2Y12 reaction units (PRU), aspirin reaction units (ARU) and P2Y12 % inhibition value were significantly decreased in the triple antiplatelet therapy group than those of the dual antiplatelet therapy group(P<0.05). The time interval of loading doses, dose-to-PCI time were 10.2 hours (95% CI: 7.4-13.1 hours) in the triple antiplatelet therapy group, and 7.8 hours (95% CI: 4.5-11.2 hours) in the dual antiplatelet therapy group. The HPR rates were significantly reduced in the triple antiplatelet therapy group than those of the dual platelet therapy group before coronary interventin (83.3% and 46.7%, P=0.003), at 24 hours (36.7% and 13.3%, P=0.018) and 30 days (40.0% and 16.7%, P=0.045) after coronary intervention. During the 30 days' follow-up period, 2 cases of in-stent thrombosis were found in the dual antiplatelet therapy group and received coronary revascularization; no cardiac death, ischemic stroke and bleeding complications was found. There was no significant difference in the incidence of secondary end points between two groups (P>0.05). **Conclusion:** Adjunctive 200 mg cilostazol in addition to the dual antiplatelet therapy could significantly reduce the incidence of HPR after coronary stent intervention.

Key words: Cilostazol; Platelet; Drug-eluting stents

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前言

目前,冠脉介入治疗指南建议接受冠脉内支架植入术的患者服用两联抗血小板聚集治疗(阿司匹林及氯吡格雷),但未能彻底预防术后主要心脑血管事件的发生。虽然,国外冠脉介入治疗指南提议用普拉格雷替代氯吡格雷进行抗血小板聚集治

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疗,但普拉格雷在降低冠状动脉支架植入术后血小板高反应性(high post-treatment platelet reactivity,HPPR)的同时增加了出血并发症的风险性,尤其是对老年患者。在国内普拉格雷尚未上市的情况下,高剂量的氯吡格雷负荷剂量治疗(600 mg/150 mg)可以在一定程度上降低 HPPR 的发生率,但个体差异所致的药物抵抗性使高剂量的氯吡格雷负荷剂量治疗尚不能完全克服 HPPR 的发生。多项临床研究结果表明 HPPR 与经皮冠状动脉介入治疗(percutaneous coronary intervention,PCI)后主要心脑血管事件的发生密切相关。

为了降低 HPPR,有关临床研究结果表明在两联抗血小板聚集治疗(阿司匹林及氯吡格雷)的基础上附加 200 mg 西洛他唑可以降低血小板的高反应性。但到目前为止,有关西洛他唑在血小板聚集治疗方面的临床研究大多数是以术后附加西洛他唑作为维持量治疗为主,尚无有关术前附加西洛他唑负荷剂量治疗的相关研究。本研究旨在研究拟行冠脉支架植入术的老年患者术前在两联抗血小板聚集药物负荷剂量治疗基础上加用 200 mg 西洛他唑负荷剂量与传统的两联抗血小板治疗比较,是否具有降低 HPPR 的叠加效应及减少术后 30 天内主要心脑血管事件及出血并发症的作用,为下一步大规模随机化临床实验的实施获取有力的客观依据。

1 资料与方法

1.1 实验设计及研究对象

2011 年 9 月至 2012 年 9 月,在哈尔滨医科大学第四附属医院心内科住院需择期 PCI 治疗的 60 名老年患者入选本研究。实验对象的入选标准如下:1)60 岁至 80 岁之间的老年患者;2)择期行冠脉内药物洗脱支架植入术的冠心病患者;3)知晓本实验流程并在实验研究同意书上签名的患者。实验对象的排查标准:1)60 岁以下,80 岁以上的患者;2)ST 段抬高型心肌梗死发作时间在 12 小时以内者;3)合并严重肾功能不全者(血肌酐 >2.5 mg/dL);4)近 6 个月内有胃肠道出血史及脑血管疾病史者;5) 术中使用糖蛋白Ⅱb/Ⅲa 抑制剂的患者;6) 血小板计数 <80000/L 或血红蛋白 <8.0 g/dL;7) 术后需华法林抗凝治疗者;8)对阿司匹林、氯吡格雷及西洛他唑有过敏倾向者;9)参加本实验前 2 个月内服用过任何与本实验无关的实验性药物者。

将所有患者随机分为三联抗血小板治疗组(n=30)和两联抗血小板治疗组(n=30)。至少在术前 3 小时内,患者接受负荷剂量治疗(300 mg 阿司匹林及 300 mg 氯吡格雷,附加或未附加 200 mg 西洛他唑),且术后 12 小时起服用了维持剂量(阿司匹林 75 mg/d 及氯吡格雷 75 mg/d, 附加或未附加西洛他唑 100 mg,bid)。此外,在术前、术后 24 小时及术后 30 天,对每例术后患者实施了血小板聚集试验(图 1)。

1.2 血小板的功能测定

每个样品置于 3.2%柠檬酸钠真空试管内,并在 60 分钟内利用光学比浊法(light transmittance aggregometry,LTA)及 VerifyNow 血小板分析仪检测血小板的反应性。应用 LTA 血小板分析仪检测 10 μM 二磷酸腺苷 (adenosine diphosphate,ADP)及 0.5 μM 花生四烯酸(arachidonic acid,AA)诱导下的血小板聚集率。LTA 结果显示为 6 分钟内最高血小板聚集率(maximum platelet aggregation,MPA)。VerifyNow 血小板分析仪的结果显示为 P2Y12 reaction units (PRU)、P2Y12 % inhibition 及 aspirin reaction units(ARU)。

1.3 主要终点

主要终点为术后 HPPR 的发生率。HPPR 定义为 P2Y12 % inhibition 数值小于 20%。次要终点为术后 30 天内主要心脑血管事件(心源性死亡、非致死性心肌梗死、缺血性卒中、紧急血运重建及支架血栓)及出血性事件的发生率。

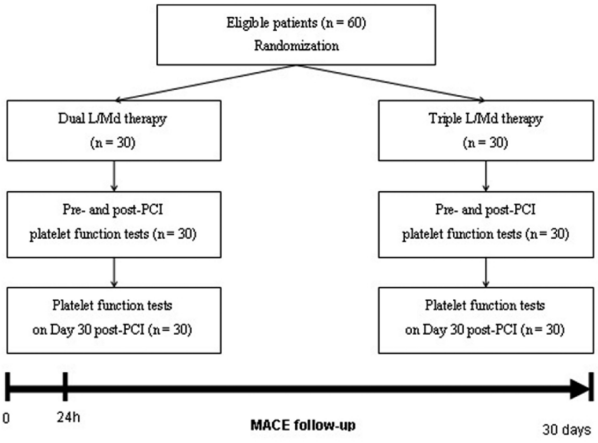

图 1 研究流程图

Fig.1 The flow chart

Note: L/Md: loading/maintenance-dose; PCI: percutaneous coronary intervention.

1.4 统计学分析

应用 SPSS15.0 软件进行所有统计学分析。计量资料用 mean(SD),组间比较采用 t 检验。计数资料用频率(百分比)表示,组间比较采用卡方检验,如果 2× 2 表的期望频数 <5,则采用 Fisher 精确检验。以 P<0.05 为差异具有显著性意义。

2 结果

2.1 两组患者的基线资料比较

2011 年 9 月至 2012 年 9 月, 共 60 例老年患者入选了本次研究,每组各 30 例。患者的基线临床情况、病变及介入治疗特征见表。两组的性别构成、年龄、危险因素、实验室检查、冠脉所见及介入特点方面均无显著性差异(P>0.05),见表 1。

2.2 两组患者的血小板聚集率比较

LTA 检测结果显示三联抗血小板治疗组较两联抗血小板治疗组明显降低 10μM ADP 诱导的 MPA, 但是两组 0.5 μM AA 诱导的 MPA 之间无显著性差异 (P>0.05), 见图 2。VerifyNow 血小板分析仪检测结果显示三联抗血小板治疗组的 PRU、ARU 及 P2Y12 % inhibition 值均较两联抗血小板治疗组显著降低,差异具有统计学意义(P<0.05),图 3。

2.3 两组患者 HPPR 的发生率比较

三联抗血小板治疗和两联负荷剂量的抗血小板治疗的给药时间 (第一次投药至冠脉介入治疗的时间间隔) 分别为 10.2 小时(95%可信区间:7.4-13.1 小时)和 7.8 小时(95%可信区间:4.5-11.2 小时), 三联抗血小板治疗组术前 HPPR (83.3%和 46.7%, P=0.003)、术后 24 小时(36.7%和 13.3%,P=0.018)及术后 30 天 HPPR (40.0%和 16.7%, P=0.045)的发生率均较两联抗血小板治疗组明显降低(P<0.05)。

表 1 两组患者的基线资料比较

Table 1 Comparison of the baseline information between two groups

Variables	Dual L/Md therapy (n=30)	Triple L/Md therapy (n=30)	p-value
Age (years)	69.1(9.7)	69.5 (9.8)	0.510
Gender(Male/Female)	21/9	16/14	0.184
BMI(kg/m^2)	24.1 (2.8)	24.7 (3.3)	0.504
Diagnosis			0.700
Stable angina (SA)	2 (6.7%)	2 (6.7%)	
Unstable angina (UA)	18 (60%)	22 (73.3%)	
NSTEMI	8 (26.7%)	5 (16.7%)	
STEMI	2 (6.7%)	1 (3.3%)	
Risk factor, n(%)			
Diabetes Mellitus	16 (53.3%)	11 (36.7%)	0.194
Hypertension	20 (66.7%)	14 (46.7%)	0.118
Active Smoker	10 (33.3%)	9 (30.0%)	0.781
Hyperlipidemia	5 (16.7%)	12 (40.0%)	0.045
Pre-PCI, n(%)	9 (30.0%)	8 (26.7%)	0.774
Pre-MI, n(%)	11 (36.7%)	5 (16.7%)	0.080
Pre-stroke, n(%)	1 (3.3%)	2 (6.7%)	0.554
Hemoglobin(g/dL)	12.8 (1.8)	13.4 (1.8)	0.182
WBC count(10^3/μL)	7.38 (2.32)	7.82 (2.35)	0.459
Platelet count(10^3/μL)	210.9 (62.3)	228.7 (50.3)	0.229
Angiographic diagnosis			0.107
1-VD, n (%)	10 (33.3%)	6 (20.0%)	
2-VD, n (%)	8 (26.7%)	16 (53.3%)	
3-VD, n (%)	12 (40.0%)	8 (26.7%)	
Target lesion			0.792
LAD, n (%)	15 (50.0%)	13 (43.3%)	
LCx, n (%)	3 (10.0%)	5 (16.7%)	
RCA, n (%)	9 (30.0%)	10 (33.3%)	
LMCA, n (%)	2 (6.7%)	2 (6.7%)	
Ramus artery, n (%)	1 (3.3%)	0	
Number of stents used	1.6 (0.8)	1.6 (0.8)	NS

Note: BMI indicates body mass index; LAD, left anterior descending coronary artery; LCx, left circumflex artery; L/Md, loading/maintenance-dose; LMCA, left main coronary artery; NS, not significant; NSTEMI, non ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; VD, vessel disease; and WBC, white blood cells.

2.4 两组的临床终点比较

在术后 30 天的随访观察期间，两联抗血小板治疗组 2 例患者出现支架内血栓，并进行了血运重建术；无 1 例心源性死亡、缺血性卒中及出血性并发症的发生。两组次要终点的发生率比较无显著性差异(P>0.05)。

3 讨论

本研究结果显示术前及术后附加 200 mg 西洛他唑的三联抗血小板治疗可以显著降低 HPPR 的发生率。西洛他唑降低血小板高反应性的可能机制如下：1)通过抑制血小板内磷酸二酯酶活性，增加血小板内 cAMP 浓度；2)改善损伤的血管内皮功能及减少血液循环中被激活的血小板的数目。值得注意的是，虽然两联抗血小板治疗组按 PCI 治疗指南给予了阿司匹林及氯吡格雷的负荷剂量，但是术前 HPPR 发生率仍高达 83.3%。两联抗血小板治疗组的负荷治疗剂量投药平均投药时间为 7.8 小时(95%可信区间：4.5-11.2 小时)，其术前较高的 HPPR 发生率可能与负荷剂量投药时间过短有关。CREDO 的研究结果提示 300 mg 氯吡格雷负荷剂量应在 PCI 术前 15 至 24 小时之间服用时才能到达有效的治疗浓度，从而达到提高临床预后的目的。Motosaka 等的研究表明，即使投放 600 mg 氯吡格雷的负荷剂量处方，其最大抗血小板聚集效果也在服用 24 小时后出现。根据 Motosaka 等实验结果，在 PCI 术前 6 至 24 小时内服用 600 mg 氯吡格雷负荷剂量的患者术前 HPPR 的发生率也高达 75%。因此，PCI 术前单纯服用 300 mg 负荷剂量的阿司匹林及氯吡格雷很难达到有效的抗血小板聚集治疗，尤其对于需要急诊 PCI 治疗的急性冠脉综合征的患者。

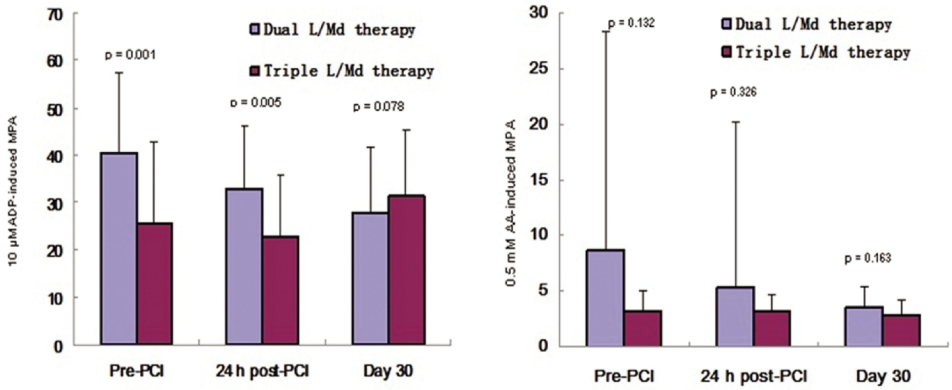

图 2 两组 PCI 术前和术后的 LTA 结果比较

Fig.2 Comparison of the LTA results of pre- and post-PCI between two groups

Note: AA indicates arachidonic acid; ADP, adenosine diphosphate; L/Md, loading/maintenance-dose; MPA, maximum platelet aggregation; PCI: percutaneous coronary intervention; Pre-PCI, platelet function tests performed just before PCI; 24 h post-PCI, platelet function tests performed at 24 h after PCI.

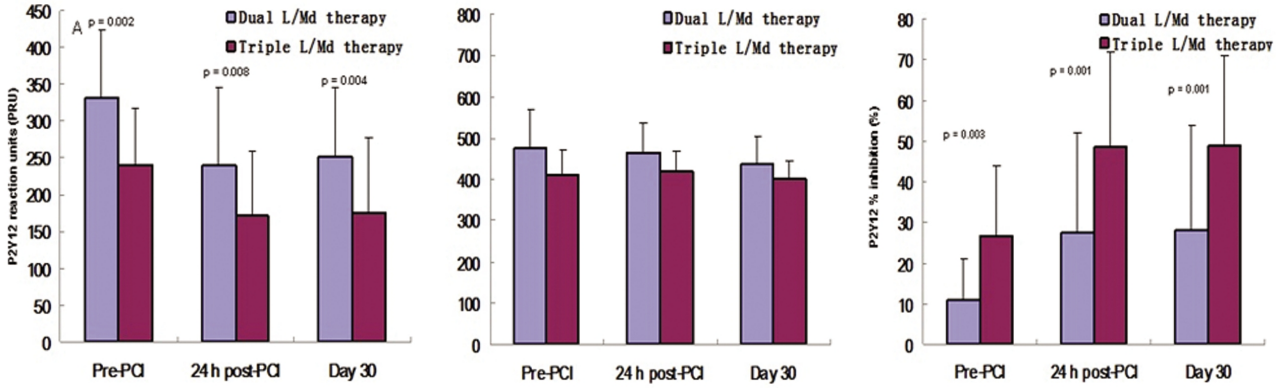

图 3 PCI 术前术后 VerifyNow assays 的结果比较

Fig.3 Comparison of the Verifynow assays results of pre- and post-PCI between two groups

Note: L/Md indicates loading/maintenance-dose; PCI, percutaneous coronary intervention; Pre-PCI, platelet function tests performed just before PCI; and 24 h post-PCI, platelet function tests performed at 24 h after PCI.

目前，研究已证实 HPPR 与不良临床事件的发生有关，且降低血小板高反应性可使主要心血管事件的发生率下降。在术后 30 天的随访观察期间，两联抗血小板治疗组出现了 2 例支架内血栓合并血运重建术，但三联抗血小板治疗组未出现。虽然实验室检查结果提示三联抗血小板治疗优于两联抗血小板治疗，可能是研究对象入选数目过小而未能观察到具有显著性差异的临床事件发生率。此外，两联抗血小板治疗组在术前表现了很高的 HPPR 发生率，但未发现严重的临床心血管事件的发生率。上述问题仍有待通过大规模多中心随机性前瞻性临床研究进一步阐明。

本研究的局限性如下：①因本研究是小规模单中心实验，故难以判明两种治疗方案在预防主要心脑血管事件发生率方面的优劣，尚需要更大规模多中心随机性前瞻性临床研究进一步阐明；②两联抗血小板治疗组虽然在术前表现了很高的 HPPR 发生率，但未引起很高的临床心血管事件的发生率，故实验性确定的药物抵抗与不良的临床事件的发生之间尚不能确定有明显的线性关系。

总之，本研究结果表明在两联抗血小板聚集治疗的基础上附加 200 mg 负荷及维持剂量的西洛他唑可显著降 PCI 术前及术后 HPPR 的发生率。

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