

· 临床研究 ·

替罗非班对老年急性冠状动脉综合征患者经皮冠状动脉介入治疗围手术期应用的安全性研究

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【摘要】目的 探究经皮冠状动脉介入治疗(PCI)围手术期联合应用替罗非班抗血小板治疗,对不同年龄急性冠状动脉综合征(ACS)患者的有效性及安全性。**方法** 回顾性地收集解放军总医院老年心内科2011年1月至2012年12月确诊为ACS,围术期均用小剂量替罗非班,并植入药物洗脱支架(DES)的患者302例(男性207例,女性95例),根据年龄分为老年组(≥ 65 岁, $n = 155$)和中青年组(< 65 岁, $n = 147$)。比较两组患者PCI术后30d内主要及次要终点事件的发生率,并用多因素logistic回归分析终点事件发生的相关危险因素。**结果** (1)老年组主要终点事件发生率明显高于中青年组[26(16.7%) vs 7(4.8%), $P = 0.001$]。(2)30d随访期间两组患者均未出现颅内出血,消化道出血两组各1例,老年组发生轻微出血事件24例(15.5%),中青年组6例(4.2%), $P = 0.001$ 。(3)多因素logistic回归分析表明,年龄 ≥ 65 岁、女性、吸烟史、糖尿病、高脂血症、既往PCI史为30d内主要终点事件发生的独立危险因素。(4)女性、吸烟史、糖尿病与30d内各种出血事件成正相关,老龄、高脂血症、既往PCI史不是出血并发症发生的预测因素。**结论** 围术期应用替罗非班强化抗血小板治疗,老年组患者主要终点事件及轻微出血事件的发生率均高于中青年组,提示对老年患者介入治疗过程中强化抗血小板治疗需慎重。

【关键词】 老年人; 急性冠状动脉综合征; 经皮冠状动脉介入治疗; 替罗非班

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Safety of tirofiban in elderly patients with acute coronary syndromes in perioperative period of percutaneous coronary intervention

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【Abstract】 Objective To assess the efficacy and safety of combined application of tirofiban with percutaneous coronary intervention (PCI) in acute coronary syndromes (ACS) patients at different ages in perioperative period. **Methods** A retrospective study was carried out for consecutive ACS patients receiving low-dose tirofiban in perioperative period and undergoing PCI and drug-eluting stents (DES) implantation in our department from Jan. 2011 to Dec. 2012. A total of 302 patients (207 males and 95 females) were recruited in this study, and were divided into 2 groups according to their ages: the elderly group (≥ 65 years, $n = 155$) and the young and middle aged group (age < 65 years, $n = 147$). The incidences of primary and secondary end points of a major cardiovascular event were compared between the 2 groups within 30 d after the PCI. Multiple logistic regression analysis was used to analyze the risk factors for the endpoints. **Results** (1) Among the 302 patients, the incidence of primary end points was significantly higher in the elderly group than in the young and middle aged group [26(16.7%) vs 7(4.8%), $P = 0.001$]. (2) No serious acute intracranial bleeding occurred in the 2 groups. Each group had 1 case of gastrointestinal bleeding [1(0.7%) vs 1(0.6%), $P = 1.000$]. While, there were 24 patients (15.5%) having minimal bleeding events from the elderly group and 6 patients (4.2%) from the young and middle aged group ($P = 0.001$). (3) Multiple logistic regression analysis indicated that aged over 65 years, female, history of smoking, diabetes mellitus, hyperlipidemia, and prior history of PCI were the independent risk factors of the primary end points in both groups during the 30-day follow-up. (4) Female, history of smoking, and diabetes mellitus were positively correlated with bleeding complications, while aging, hyperlipidemia, and prior history of PCI were not the independent predictive factors of bleeding events. **Conclusion** Combined application of tirofiban in perioperative period of PCI results in significant increases in the incidences of primary end points and minimal bleeding events in the elderly than in the young and middle aged patients, which suggests

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that the antiplatelet medication of tirofiban should be prudently conducted for the elderly.

【Key words】 aged; acute coronary syndromes; percutaneous coronary intervention; tirofiban

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鉴于老龄人口在全球的快速增长,老年患者心血管疾病的发病率和死亡率越来越高。美国心脏病协会统计显示,美国 ≥ 65 岁老年患者占急性心肌梗死住院患者的60%,病死率 $> 80\%$ ^[1]。血小板活化是急性冠脉综合征(acute coronary syndromes, ACS)发病机制的关键环节^[2],公认的阿司匹林(aspirin)联合氯吡格雷(clopidogrel)双联抗血小板治疗方案仍存在着抗血小板治疗的低反应性^[3,4],在双联抗基础上加用替罗非班(tirofiban)行强化抗血小板治疗可以显著降低血小板活化率,进而预防支架内血栓形成(stent thrombosis, ST)^[5],降低心血管事件的发生率^[6]。由于老年患者具有独特的临床特征及病理生理学特性^[7],老年ACS患者是否能够同中青年患者一样在经皮冠状动脉介入治疗(percutaneous coronary interventional, PCI)围术期安全地使用强化抗血小板治疗方案,目前尚缺乏可靠的临床试验数据支持。本研究旨在评价PCI围术期在应用阿司匹林和氯吡格雷的基础上加用替罗非班行强化抗血小板治疗对老年ACS患者的临床疗效及安全性,并对相关危险因素进行分析。

1 对象与方法

1.1 研究对象

收集解放军总医院老年心内科2011年1月至2012年12月住院的临床资料,选取其中符合ACS诊断标准的患者302例纳入研究,患者住院期间均至少植入1枚药物洗脱支架(drug-eluting stents, DES),年龄38~87岁。主要排除标准(具备以下一项即排除):(1)入院时严重且未控制的高血压[SBP ≥ 180 mmHg(1mmHg=0.133kPa)/DBP ≥ 110 mmHg]或慢性严重高血压病史;(2)30d内活动性内脏出血,3个月内曾有手术、外伤、失血性疾病史,6个月内曾有脑卒中及短暂性脑缺血发作史;(3)对阿司匹林、氯吡格雷及替罗非班等抗血小板药物过敏者;(4)有出血倾向,具有抗血小板治疗禁忌证或近期拟行外科手术者;(5)严重肝肾功不全及凝血功能异常;(6)合并其他终末期疾病且预期寿命 < 1 年;(7)不同意介入治疗的患者。

1.2 分组及用药

根据年龄分为老年组(≥ 65 岁,155例)和中

青年组(< 65 岁,147例)。所有患者术前均口服阿司匹林(阿司匹林肠溶片,100mg,拜耳医药保健有限公司;初次应用者,负荷量300mg,维持量100mg/d)、氯吡格雷(75mg,赛诺菲安万特杭州制药有限公司;初次应用者,负荷量300mg,维持量75mg/d),围术期在双联抗血小板基础上加用小剂量替罗非班(盐酸替罗非班氯化钠注射液,100ml:5mg,武汉远大制药集团有限公司)行强化抗血小板治疗,小剂量替罗非班应用方案^[8]:术前替罗非班以0.40g/(kg·min)静泵30min,以后以0.1g/(kg·min)静泵24~36h。冠状动脉造影过程中,穿刺成功后一次性经鞘管推注普通肝素70~100U/kg,术中根据手术时间酌情追加用量。术后继续使用低分子肝素2~3d,双联抗血小板连续治疗30d。

1.3 疗效判定指标

记录患者的基线信息,所有患者均进行术后30d的随访,随访的方式包括电话回访、门诊随访或住院追寻获取诊疗记录的方式,记录患者服药的依从性及治疗期间主要及次要终点事件的发生率。336例入组患者实际完成随访302例,回访率为89.9%,失访原因多为患者未坚持门诊就诊,及其可联系家属已更换电话号码。

1.4 统计学处理

采用SPSS13.0进行统计学处理。正态分布的连续变量以 $\bar{x} \pm s$ 描述,两组间的比较采用独立样本 t 检验;非正态分布的连续变量以M(Q1~Q3)描述,组间比较采用Mann-Whitney U 非参数检验。分类变量以频数和百分构成比表示,采用非配对卡方检验、Fisher精确概率法进行统计学分析。采用多因素logistic回归分析主要终点事件和次要终点事件发生的相关危险因素,采用逐步回归法筛选自变量。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者基线资料比较

两组患者基线资料单因素分析结果显示,老年患者与中青年患者在性别构成、体质量指数(body mass index, BMI)水平、血甘油三酯、尿酸、高密度脂蛋白胆固醇(high density lipoprotein cholesterol,

HDL-C)、高血压、糖尿病、吸烟史、饮酒史、外周血管病、脑卒中及血管紧张素受体拮抗剂 (angiotensin receptor blockers, ARB) 的使用等方面的差异具有统计学意义 ($P < 0.05$; 表1)。

2.2 冠状动脉病变及支架植入情况

由表2可以看出, 老年组患者人均病变血管数目、双支病变及多支病变的比率要多于中青年组 ($P < 0.05$), 中青年组患者支架平均直径要明显长于老年组, 差异具有统计学意义 ($P < 0.05$; 表2)。

2.3 30d内主要终点事件的随访结果

随访的主要终点, 即有效性终点, 包括ST、主要不良心脑血管事件 (major adverse cardiac and cerebrovascular events, MACCE)、支架内再狭窄 (in-stent restenosis) 和再发心绞痛 (recurrent angina pectoris)。其中MACCE定义为心源性死亡、非致死性急性心肌梗死、脑血管事件、紧急靶病变/靶血管再次血运重建(包括PCI或冠状动脉旁路移植术)^[9]。术后30d随访发现, 两组患者主要终点事件共发生33例, 其中老年组26例 (16.7%), 中青年组7例 (4.8%), 差异具有统计学意义 ($P = 0.001$), 两组患者30d内均无脑血管事件的发生 (图1)。

2.4 30d内次要终点事件的随访结果

随访的次要终点, 即安全性终点, 包括临床的各种出血事件, 按TIMI试验^[10]和PCI的CURE研究^[11]定义为主要出血、次要出血和轻微出血。由图2可以看出, 两组患者在30d的随访期间均未发生严重的颅内出血事件, 次要出血即消化道出血事件, 两组各发生1例 [1 (0.7%) vs 1 (0.6%); $P = 1.000$], 总计30例患者发生了轻微出血事件, 且老年组轻微出血事件发生率明显高于中青年组 [24 (15.5%) vs 6 (4.2%); $P = 0.001$]。

2.5 主要终点事件及次要终点事件发生的危险因素

多因素logistic回归模型中, 将年龄、男性、BMI、高血压病、糖尿病、高脂血症、吸烟史、饮酒史、冠心病家族史、既往病史及冠状动脉病变数作为自变量, 以30d内是否发生主要及次要终点事件为因变量, 采用多因素logistic回归分析终点事件发生的危险因素。结果提示, 年龄 ≥ 65 岁、女性、吸烟史、糖尿病、高脂血症、既往PCI史为总人群30d内发生主要终点事件的危险因素 (表3), 女性、吸烟史、糖尿病为总人群30d内发生次要终点事件的独立预测因子 (表4)。

表1 两组患者基线资料
Table 1 Baseline clinical characteristics of patients in the two groups

Item	Elderly group (n = 155)	Young and middle aged group(n = 147)
Age(years, $\bar{x} \pm s$)	74.1 \pm 5.24**	57.24 \pm 6.39
Male[n(%)]	86 (55.5)**	121 (82.3)
Body mass index (kg/m ² , $\bar{x} \pm s$)	25.67 \pm 3.06*	26.57 \pm 3.33
LVEF(% , $\bar{x} \pm s$)	60.43 \pm 8.03	59.97 \pm 6.86
LVEdD(mm, $\bar{x} \pm s$)	45.68 \pm 5.21	46.59 \pm 4.94
Laboratory analyses		
TC(mmol/L, $\bar{x} \pm s$)	4.21 \pm 1.17	4.32 \pm 1.30
TG(mmol/L, $\bar{x} \pm s$)	1.56 \pm 0.89**	2.04 \pm 1.38
LDL-C(mmol/L, $\bar{x} \pm s$)	2.53 \pm 0.92	2.44 \pm 0.93
HDL-C(mmol/L, $\bar{x} \pm s$)	1.11 \pm 0.27**	1.00 \pm 0.24
Serum creatinine (μ mol/L, $\bar{x} \pm s$)	76.67 \pm 27.11	74.89 \pm 18.73
Urea nitrogen (mmol/L, $\bar{x} \pm s$)	5.68 \pm 1.82	5.36 \pm 1.42
Uric acid (μ mol/L, $\bar{x} \pm s$)	327.3 \pm 110.8**	356.8 \pm 140.5
Risk factors [n(%)]		
Hypertension	110 (71.0)**	78 (53.1)
Diabetes mellitus	91 (58.7)*	67 (45.6)
Hyperlipidemia	101 (65.2)	104 (70.7)
History of smoking	48 (31.0)**	71 (48.3)
History of alcohol abuse	29 (18.7)**	54 (36.7)
Family history of CAD	13 (8.4)	21 (14.3)
Past medical history[n(%)]		
Prior MI	31 (20.0)	33 (22.4)
Prior PCI	38 (24.5)	33 (22.4)
Prior CABG	0 (0.0)	0 (0.0)
PVD	47 (30.3)**	16 (10.9)
CVD	34 (21.9)*	17 (11.6)
COPD	6 (3.9)	2 (1.4)
CKD	3 (1.9)	3 (2.0)
Clinical presentation [n(%)]		
UA	139 (89.7)	125 (85.0)
STEMI	13 (8.4)	20 (13.6)
NSTEMI	3 (1.9)	2 (1.4)
Medications[n(%)]		
β -blockers	75 (48.4)	87 (59.2)
ACEIs	14 (9.0)	19 (12.9)
ARBs	55 (35.5)**	30 (20.4)
CCBs	76 (49.0)	62 (42.2)
Statins	146 (94.2)	134 (91.2)
Nitrates	143 (92.3)	130 (88.4)

LVEF: left ventricular ejection fraction; LVEdD: left ventricular end-diastolic diameter; TC: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; PVD: peripheral vascular diseases; CVD: cerebral vascular diseases; COPD: chronic obstructive pulmonary disease; CKD: chronic renal disease; UA: unstable angina; STEMI: ST-elevation myocardial infarction; NSTEMI: non ST-elevation myocardial infarction; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCB: calcium channel blocker. Compared with young and middle aged group, * $P < 0.05$, ** $P < 0.01$

表2 两组患者冠状动脉造影及支架植入情况

Table 2 Baseline angiographic outcomes and lesion characteristics in two groups

Item	Elderly group (n = 155)	Young and middle aged group(n = 147)
Number of stents per patient (n, $\bar{x} \pm s$)	2.53 ± 1.78	2.40 ± 1.46
Number of treated vessels per patient(n, $\bar{x} \pm s$)	2.54 ± 0.71**	2.27 ± 0.76
Mean stent length (mm, $\bar{x} \pm s$)	22.96 ± 5.33	23.37 ± 5.27
Mean stent diameter (mm, $\bar{x} \pm s$)	2.96 ± 0.40**	3.11 ± 0.46
Number of involved vessels [n(%)]		
Single-vessel disease	20 (12.9)	28 (19.0)
Double-vessel disease	31 (20.0)**	52 (35.4)
Multivessel disease	104 (67.1)**	67 (45.6)
Coronary artery stented [n(%)]		
LMT	5 (3.2)	1 (0.7)
LAD	161 (40.7)	167 (47.7)
LCX	94 (23.8)	64 (18.3)
RCA	135 (34.2)	118 (33.7)

LMT: left main trunk; LAD: left anterior descending branch; LCX: left circumflex artery; RCA: right coronary artery. Compared with young and middle aged group, **P < 0.01

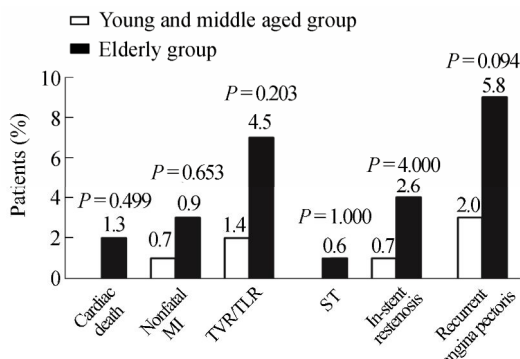


图1 两组患者术后30d随访的主要终点(有效性终点)事件
Figure 1 The efficacy endpoint at 30d follow-up after PCI in two groups
MI: myocardial infarction; TVR/TLR: target vessel revascularization/target lesion revascularization; ST: stent thrombosis

表3 主要终点事件多因素logistic回归分析

Table 3 Multivariate logistic regression analysis of the efficacy endpoint

Variable	B	S.E.	Wald	OR(95%CI)	P value
Age	1.161	0.550	4.465	3.194 (1.088-9.377)	0.035
Male gender	1.538	0.600	6.570	4.654 (1.436-15.081)	0.010
Smoking	2.193	0.581	14.223	8.960 (2.867-28.003)	0.000
DM	1.136	0.551	4.242	3.113 (1.056-9.175)	0.039
Hyperlipidemia	1.678	0.789	4.519	5.355 (1.140-25.153)	0.034
Prior PCI	1.564	0.446	12.321	4.778 (1.995-11.442)	0.000

DM: diabetes mellitus; PCI: percutaneous coronary intervention; B: partial regression coefficient; S.E.: standard error; Wald Chi-Square; OR (95% CI): Odds Ratio (95% confidence interval)

表4 次要终点事件多因素logistic回归分析

Table 4 Multivariate logistic regression analysis of the safety endpoint

Variable	B	S.E.	Wald	OR(95%CI)	P value
Male gender	2.160	0.489	19.542	8.669 (3.327-22.584)	0.000
Smoking	2.299	0.501	21.089	9.963 (3.735-26.578)	0.000
DM	1.092	0.542	4.064	2.982 (1.031-8.624)	0.044

DM: diabetes mellitus; B: partial regression coefficient; S.E.: standard error; Wald: Wald Chi-Square; OR(95%CI): Odds Ratio (95% confidence interval)

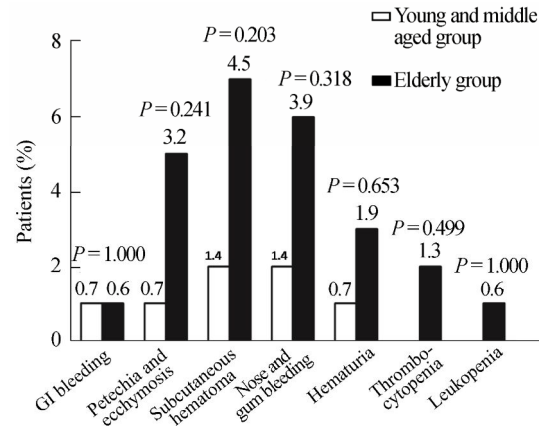


图2 两组患者术后30d随访的次要终点(安全性终点)事件
Figure 2 The safety endpoint at 30d follow-up after PCI in two groups
GI bleeding: gastrointestinal bleeding; PCI: percutaneous coronary intervention

3 讨论

本研究将ACS患者按年龄分为了老年组(年龄≥65岁)和中青年组(年龄<65岁),在对两组患者基线资料及冠状动脉造影支架植入情况进行单因素分析比较的基础上,对两组患者主要及次要终点事件的发生情况进行了PCI术后30d的随访,并对相关危险因素进行了多因素回归分析。统计结果表明,随着年龄的增长,女性ACS患者的比率增加,高血压、糖尿病、外周血管病、脑卒中等发病率逐渐增高,老年组患者人均病变血管数目及双支病变、多支病变的比率要多于中青年组,各种危险因素共同促使不同年龄段的ACS患者基线资料及冠状动脉造影结果有显著差异。

替罗非班常见的不良反应是出血和血小板减少^[12],随着年龄增大,不良反应发生风险亦增加。

Sinnaeve等^[13]对6 095例平均年龄61岁(13%≥75岁)老年ST段抬高型心肌梗死患者进行研究发现, <75岁患者联合应用血小板GP II b/III a受体拮抗剂阿昔单抗可获益, 而≥75岁高龄患者联合应用阿昔单抗30d内死亡、院内再梗死及难治性心肌缺血等复合终点事件发生的风险均显著增加。Song^[14]为研究替罗非班在治疗老年ACS中的安全性, 共纳入200例老年患者随机分为对照组(肝素)和试验组(肝素+替罗非班)两组, 研究结果表明试验组一级终点事件(包括死亡和心肌梗死)比对照组降低, 但出血发生率较对照组显著增多。本研究也发现老年组患者应用替罗非班强化抗血小板治疗, 主要终点事件及轻微出血事件发生率均较中青年组增多, 且差异具有统计学意义。因此, 临床上老年ACS患者应用GP II b/III a受体拮抗剂, 需要更加重视其安全性, 权衡出血风险及获益, 个体化治疗, 随时调整治疗策略。

进一步对主要终点事件进行多因素回归分析发现, 年龄、性别、吸烟史、糖尿病、高脂血症、既往PCI史为总人群30d内发生主要终点事件的危险因素, 而性别、吸烟史、糖尿病与出血并发症密切相关, 这与国外研究类似。欧洲EUROASPIRE I研究^[15]通过对9个欧洲国家≤70岁的3 343例冠心病患者进行多因素生存分析后发现, 吸烟和糖尿病是冠心病患者心血管疾病死亡率、冠心病死亡率的强有力的预测因子。Volzke等^[16]对1 038例冠心病人群进行了(6.4±1.8)年的随访, 发现死亡事件发生的主要预测因素包括年龄、脉压、吸烟史、糖尿病、血清LDL-C水平、LVEF和既往心肌梗死病史, 而高血压病对预后却无显著影响。Alexander等^[17]研究发现, 无论是应用血小板GP II b/III a受体拮抗剂治疗, 女性患者各种出血事件发生率均高于男性, 在接受血小板GP II b/III a受体拮抗剂治疗的女性患者中表现得更加显著。这些研究结果再次证实了戒烟、严格控制血糖、血脂水平有利于冠心病的预防, 也能改善冠心病患者的预后, 在冠心病二级预防中占据着重要的地位。

本研究纳入的老年组患者年龄在65~87岁之间, 并且在性别构成、高血压、2型糖尿病、外周血管病、脑卒中等方面都与中青年组有显著差异, 老年组患者冠心病危险因素更多, 冠状动脉基础病变较重, 治疗难度大, 这可能是老年ACS患者介入治疗围术期应用替罗非班30d内主要终点事件及轻微出血事件发生率较中青年组增多的原因。本研究还发现替罗非班并未增加老年组严重出血的发生率,

仅轻微出血事件有所增加, 且停用替罗非班等药物后得到改善, 说明老年PCI患者给予替罗非班是安全有效的。由于年龄是PCI术后发生主要不良心血管事件及出血事件的重要影响因素, 老年患者强化抗血小板治疗的获益与出血风险之间的权衡更应慎重, 不同年龄段的患者介入治疗过程中强化抗血小板方案要有一定差异, 严格把握适应证, 谨慎选择应用。

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