·临床研究·

半量替罗非班在老年冠状动脉旁路移植术前过渡期应用的疗效及安全性分析

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【摘 要】目的 探讨半量的血小板GpⅡb/Ⅲa受体拮抗剂替罗非班（tirofiban）在老年冠状动脉旁路移植术（CABG）前过渡期应用的疗效和安全性。**方法** 入选2012年1月1日至2014年12月31日就诊于泰山医学院附属菏泽市立医院并诊断为非ST段抬高的急性冠状动脉综合征（NSTE-ACS）、经冠状动脉造影（CAG）证实为严重的三支病变和（或）左主干病变并需外科CABG的患者117例。患者年龄60～75（67.76±3.07）岁。停止双联抗血小板药物治疗后，采用随机数字法将患者分为半量替罗非班+低分子肝素（LMWH）组（A组，60例）和单纯LMWH组（B组，57例）。其中，A组造影后持续应用半量替罗非班至术前12h停用；B组仅单纯使用LMWH；所有患者造影后给予LMWH皮下注射至术前24h，并予常规药物治疗。比较两组患者的基线资料、过渡期主要不良心血管事件（MACE，如顽固性心绞痛发作、非致死性心肌梗死、恶性心律失常及心脏性死亡等）和出血情况。**结果** 加用替罗非班组和单纯LMWH组比较，患者的基线资料差异无统计学意义（$P>0.05$）。过渡期主要不良心血管事件中，顽固性心绞痛发作差异有统计学意义[33.3%（20/60） *vs* 57.9%（33/57），$P=0.01$]，加用替罗非班组较单纯LMWH组减少；加用替罗非班组非致死性心肌梗死、恶性心律失常及心脏性死亡事件的发病人数较单纯LMWH组减少。术前加用替罗非班组发生轻微出血2例（鼻出血1例、痔疮出血1例），单纯LMWH组发生轻微出血1例（为牙龈出血），术中出血量及术后输血量两组比较差异均无统计学意义[术中：（564.17±125.58） *vs* （542.46±94.46）ml，$P=0.30$；术后：（4.63±1.40） *vs* （4.39±1.28）u，$P=0.32$]。**结论** 对于拟行CABG的NSTE-ACS老年患者术前持续加用替罗非班组较单纯使用LMWH作为过渡，可以有效降低心血管事件，且不增加围手术期的出血风险。

【关键词】替罗非班；冠状动脉旁路移植术；有效性；安全性

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Efficacy and safety of half-dose tirofiban in elderly patients during preoperative period of coronary artery bypass grafting

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【Abstract】 Objective To investigate the efficacy and safety of half-dose tirofiban, a platelet glycoprotein Ⅱb/Ⅲa receptor antagonist, in the elderly patients during preoperative transition period before receiving coronary artery bypass grafting. **Methods** A total of 117 patients [aged 60−75(67.76±3.07) years] with non-ST segment elevation acute coronary syndrome(NSTE-ACS) admitted to our hospital from January 2012 to December 2014 were enrolled in this study. All the patients were diagnosed as three-vessel disease and/or left main coronary diseases by coronary arteriography, and required surgical treatment of coronary artery bypass grafting (CABG). Upon termination of dual antiplatelet therapy, the cohort was randomly divided into half-dose tirofiban plus low molecular weight heparin (LMWH) group (group A, $n=60$), and simple LMWH group (group B, $n=57$). The patients of group A were subjected to half-dose tirofiban after coronary arteriography till 12h before the surgery and subcutaneous injection of LMWH till 24h before surgery. While those of group B only received subcutaneous injection of LMWH as in group A. Additionally, conventional medical treatment was also given to each patient. The following parameters were compared between the 2 groups, including baseline levels, bleeding, as well as major adverse cardiovascular events (MACE) during transition period, such as intractable angina, nonfatal myocardial

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infarction, malignant arrhythmia and cardiac death. **Results** No significant difference was found in the baseline data between the 2 groups ($P > 0.05$). For the MACEs, the incidence of intractable angina was lower in group A than in group B [33.3% (20/60) *vs* 57.9% (33/57), $P = 0.01$], and so were those of nonfatal myocardial infarction, malignant arrhythmia and cardiac death, though no significant difference was observed ($P > 0.05$). In group A, epistaxis ($n = 1$) and hemorrhoidal bleeding ($n = 1$) was noted, while in group B, 1 case with gum bleeding was seen. No statistical difference was observed in the amounts of bleeding during and after operation between the 2 groups [intra-operative: (564.17 ± 125.58) *vs* (542.46 ± 94.46)ml, $P = 0.30$; post-operative (4.63 ± 1.40) *vs* (4.39 ± 1.28)u; $P = 0.32$]. **Conclusion** Compared with simple LMWH, continued preoperative administration of half-dose tirofiban in combination with LMWH can effectively decrease the incidence of adverse cardiovascular events, but have no effect on the bleeding volume during peri-operative period in the elderly NSTE-ACS patients undergoing CABG.

【**Key words**】 tirofiban; coronary artery bypass grafting; efficacy; safety

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经冠状动脉造影（coronary artery angiography，CAG）证实为严重的三支血管病变和（或）左主干病变者，往往需要通过冠状动脉旁路移植术（coronary artery bypass grafting，CABG）完成血运重建。对于非ST段抬高的急性冠状动脉综合征（non-ST segment elevation acute coronary syndrome，NSTE-ACS）的患者，临床上常规使用双联抗血小板药物（如阿司匹林和氯吡格雷），但为了避免CABG术中的出血风险，美国心脏病学会基金会/美国心脏联合会（American College of Cardiology Foundation/American Heart Association，ACCF/AHA）和欧洲心脏病协会（European Society of Cardiology，ESC）2011NSTE-ACS指南建议在实施直视手术前1周左右开始停用抗血小板药物，同时可用替罗非班作为替代，但证据不充分[1−4]。国内在停药期间仅用抗凝血药低分子肝素（low molecular weight heparin，LMWH）作为过渡，但由于缺少抗血小板药物保护，常导致患者发生主要不良心血管事件（major adverse cardiovascular events，MACE）的风险增加[5−8]。因此需要寻找半衰期短、作用可逆的抗血小板药物来缩短过渡期，减少心脏事件的发生，且达到外科直视手术出血风险的目的。我院近年来应用半量的血小板糖蛋白Ⅱb/Ⅲa（glycoprotein Ⅱb/Ⅲa，GpⅡb/Ⅲa）受体拮抗剂替罗非班（欣维宁；tirofiban）作为老年患者在冠心病监护病房CABG过渡期的抗血小板治疗药物，现总结如下。

1 对象与方法

1.1 研究对象

选择2012年1月1日至2014年12月31日于泰山医学院附属菏泽市立医院因NSTE-ACS入院治疗、经CAG证实为严重的三支病变和(或)左主干病变、并施行CABG的老年患者共117例。其中男性76例，女性41例。入选标准：NSTE-ACS患者，经CAG证实为严重的三支血管病变或左主干病变；由心内科及心外科共同研究决定且患者同意接受CABG治疗者；年龄60～75（67.76 ± 3.07）岁。排除标准：心功能Killip分级≥Ⅲ级；既往重大手术及外伤史、出血性疾病史、脑血管意外史、凝血疾病、严重贫血（治疗后Hb < 9g/L）和血小板减少症病史；严重的肝肾功能障碍(治疗后肝酶 > 正常上限的2倍，肌酐清除率（creatinine clearance rate，Ccr < 50ml/min）；对替罗非班、LMWH、阿司匹林、氯吡格雷过敏或存在药物使用禁忌证。所有患者均签署知情同意书。

1.2 药物治疗研究方法

117例患者随机分为半量替罗非班 + LMWH组（$n = 60$）和单纯LMWH（$n = 57$）。于CAG后停用双联抗血小板药物，A组以0.075μg/（kg·min）持续静脉泵入半量替罗非班至术前12h，同时给予皮下注射LMWH 100IU/kg，12h/次，至术前24h停用，B组仅单纯使用皮下注射LMWH 100IU/kg，12h/次，至术前24h停用，两组均常规服用其他相关药物，包括他汀类降血脂药、血管紧张素转换酶抑制剂或血管紧张素受体阻断剂、β−受体阻滞剂、钙离子拮抗剂、硝酸酯类药物及质子泵抑制剂等，剂量根据临床情况调整。

1.3 观察指标

基础临床和造影资料、整体量化评估冠状动脉病变复杂程度的SYNTAX（Synergy between Percutaneous Coronary Intervention Taxus and Cardiac Surgery）研究评分、全球急性冠状动脉事件注册（Global Registry of Acute Coronary Events，GRACE）评分及NSTE-ACS患者院内出血风险的CRUSADE（Can Rapid Risk Stratification of Unstable Angina Suppress

Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines）评分；住院期间MACE（顽固性心绞痛发作、非致死性心肌梗死、恶性心律失常及心脏性死亡）、术前出血事件、术中出血量及术后输血量。出血的定义按心脏梗死溶栓（thrombolysis in myocardial infarction，TIMI）试验协作组的定义分为：（1）主要出血：颅内出血或临床可见出血（包括影像学）伴血红蛋白浓度下降≥5g/dl；（2）小出血：临床可见出血伴血红蛋白浓度下降3～5g/dl；（3）轻微出血：临床可见出血伴血红蛋白浓度下降 < 3g/dl。

1.4 统计学处理

数据处理采用SPSS17.0软件包完成，连续性资料用$\bar{x} \pm s$表示，主要检测指标均进行正态性检验，对于偏态分布的资料经对数转换达到近似正态分布。计量资料两组比较采用t检验；计数资料以百分率表示；组间比较采用χ^2检验。以$P < 0.05$为差异具有统计学意义。

2 结 果

2.1 两组患者基础临床和冠状动脉病变情况比较

两组患者基线资料单因素分析结果显示，加用替罗非班组与单纯LMWH组患者在年龄、性别构成、体质量指数（body mass index，BMI）、高血压、2型糖尿病、血脂异常、血肌酐（serum creatinine，Scr）及肌酐清除率（creatinine clearance rate，Ccr）、吸烟、冠状动脉病变、SYNTAX评分情况、左室射血分数（left ventricular ejection fraction，LVEF）、GRACE及CRUSADE评分等方面的差异均无统计学意义（$P > 0.05$；表1）。

2.2 两组患者住院期间主要不良心血管事件比较

加用替罗非班组较单纯LMWH组患者顽固性心绞痛发作人数比较[33.3%（20/60）*vs* 57.9%（33/57），$P = 0.01$]，差异有统计学意义（$P < 0.05$）。其他发病人数比较：单纯使用LMWH组非致死性心肌梗死2例（3.5%）、恶性心律失常1例（1.8%）及心脏性死亡1例（1.8%），加用替罗非班组较单纯使用LMWH组发病数均有所减少。

2.3 两组患者出血事件比较

加用替罗非班组术前发生轻微出血2例（包括鼻出血1例，痔疮出血1例）；单纯LMWH组发生轻微出血者1例，为牙龈出血。术中出血量[（564.17 ± 125.58） *vs* （542.46 ± 94.46）ml，$P = 0.30$]及术后输血量[（4.63 ± 1.40）*vs*（4.39 ± 1.28）u，$P = 0.32$]比较，差异均无统计学意义（$P > 0.05$）。

3 讨 论

NSTE-ACS是心血管科常见的急重症，其在近年来的发病率在不断升高。临床研究证实NSTE-ACS患者已占到总出院ACS患者的3/4[9]。这当中有相当比例是三支病变和（或）左主干病变，尤其SYNTAX积分较高的患者，需要行CABG实现血管重建[10–12]。然而，NSTE-ACS发生后，往往常规给予患者双联抗血小板治疗，而它们均为长效不可逆抗血小板药物，CABG术前5～7d内服用会明显

表1 患者基线临床资料

Table 1 Clinical characteristics of patients

Item	Tirofiban + LMWH group (n = 60)	LMWH group (n = 57)	P
Male[n(%)]	39 (65.0)	37 (64.9)	0.57
BMI(kg/m^2, $\bar{x} \pm s$)	24.73 ± 2.44	24.96 ± 2.35	0.44
Hypertension[n(%)]	44 (73.3)	41 (71.9)	0.51
T2DM[n(%)]	24 (40.0)	24 (42.1)	0.48
Hyperlipidemia[n(%)]	43 (71.7)	42 (73.7)	0.54
Scr > 132.6[μmol/L, n(%)]	1 (1.7)	1 (1.8)	0.73
Ccr < 80[ml/min, n(%)]	1 (1.7)	1 (1.8)	0.73
Smoking[n(%)]	31 (51.7)	30 (52.6)	0.58
Triple vessel disease[n(%)]	47 (78.3)	45 (78.9)	0.82
Left main coronary artery lesion[n(%)]	39 (65.0)	38 (66.7)	0.91
After radiography LVEF[%, $\bar{x} \pm s$]	52.03 ± 2.51	53.04 ± 3.05	0.56
SYNTAX score($\bar{x} \pm s$)	33.80 ± 7.11	34.01 ± 7.15	0.87
GRACE risk score($\bar{x} \pm s$)	133.25 ± 25.34	135.33 ± 20.28	0.63
CRUSADE score($\bar{x} \pm s$)	31.97 ± 12.76	33.63 ± 12.19	0.47

LMWH: low molecular weight heparin; BMI: body mass index; Scr: serum creatinine; Ccr: creatinine clearance rate; T2DM: type 2 diabetes mellitus; LVEF: left ventricular ejection fraction; SYNTAX: Synergy between Percutaneous Coronary Intervention Taxus and Cardiac Surgery; GRACE: Global Registry of Acute Coronary Events; CRUSADE: Can Rapid Risk Stratification of Unstable Angina Suppress Adverse Outcomes with Early Implementation of the ACC/AHA guidelines

增加手术出血风险[13,14]。故需要半衰期短的抗血小板药物作为过渡。2011ACCF/AHA及ESC冠状动脉旁路移植术指南中均提出替罗非班可用于CABG术前过渡期抗血小板治疗。国外也有报道认为对于老年患者替罗非班可降低MACE的发生率[15]，但目前国内尚无明确的CABG术前替罗非班抗血小板治疗建议。欧美的这一方案是否适用于国人、其剂量如何把握，目前尚不明确。CABG术前的抗血小板药物的应用和停药为临床医师面临的常见问题，而且还存在一些争议。

替罗非班作为GPⅡb/Ⅲa受体的非肽类拮抗剂，通过占据GPⅡb/Ⅲa受体的结合位点，阻断纤维蛋白原与其结合，进而抑制血小板聚集的最后通路，能有效地抑制血小板聚集，由于其半衰期短（约为1.5～2h），理论上提前半天停药在心血管直视手术时抗血小板作用即基本消失。同时替罗非班还有抗炎症等抗血小板以外的作用[16]，其用于CABG术前，在有效抗血小板预防血栓事件的同时，有稳定斑块防止心脏事件发生的作用。

老年NSTE-ACS患者一般状况较年轻患者相对较差、合并症较多、病变相对复杂。对于这类患者，CABG术前突然停用抗血小板治疗，极易导致急性冠状动脉事件的发生。有研究显示，阿司匹林撤药者急性冠状动脉事件发生率为2.3%～10.2%[17]，故对于停用抗血小板治疗的患者，替罗非班是替代治疗的较好选择。但这类患者临床上抗血小板治疗出血风险相对较高，国外Song[18]的研究显示，在老年ACS患者中，替罗非班＋LWMH组一级终点事件（包括死亡和心肌梗死）比单纯LWMH组降低，但出血发生率却显著增多。国内凡永艳等[19]的研究也显示老年ACS患者，应用替罗非班抗血小板治疗，其轻微出血事件发生率增多。因此，对于老年NSTE-ACS患者，应当更加审慎使用替罗非班。本研究中两组的CRUSADE评分均处于中危，故选用半量替罗非班相对安全。两组在基础临床和造影情况方面差异无统计学意义，SYNTAX、GRACE评分显示病变程度较重，缺血风险较高。但在住院期间MACE方面，半量替罗非班组其降低顽固性心绞痛的发生率与单纯LMWH组比较显示出明显优势。这与上述研究结果一致。在非致死性心肌梗死、恶性心律失常及心脏性死亡方面，替罗非班组均表现出有所减少的趋势，但差异无统计学意义，考虑与本研究样本量偏小有关。在出血事件的发生上，本研究中替罗非班组术前出血的发生率、术中出血量及术后输血量与单纯LMWH组比较，差异均无统计学意义。说明半量应用替罗非班能有效抗血小板，降低过渡期MACE，且不增加出血风险。这些结果表明，对于我国NSTE-ACS老年患者，在CABG术前过渡期使用半量替罗非班可能是安全有效的最佳剂量。

总之，在NSTE-ACS老年患者CABG术前过渡期使用半量替罗非班可有效抗血小板，保证患者安全，术前12h停用后，血小板功能可快速恢复。该方案可能是解决过渡期无抗血小板药物保护的有用策略。但本研究病例数有限，观察时间短，其长期安全性及效果尚有待更大样本、更长随访时间的国内大规模、多中心、随机双盲试验来进一步验证。

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