·临床研究·

低剂量替格瑞洛对老年急性冠脉综合征伴慢性肾功能不全患者的疗效

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【摘 要】 **目的** 观察低剂量替格瑞洛治疗老年急性冠脉综合征(ACS)伴慢性肾功能不全(CRI)患者的疗效和安全性。**方法** 连续入选2016年10月至2017年2月解放军空军第986医院心血管内科住院治疗的≥75岁老年ACS合并CRI患者148例,根据患者服用替格瑞洛剂量不同分为低剂量替格瑞洛组(45 mg/次,2次/d,$n=52$)和标准剂量替格瑞洛组(90 mg/次,2次/d,$n=96$),口服药物3 d后行血栓弹力图(TEG)检测,比较2组患者腺苷二磷酸(ADP)诱导的血小板聚集抑制率(IPA)和随访12个月主要不良心脑血管事件(MACCE)和大出血事件的发生率。采用SPSS 19.0统计软件对数据进行分析。组间比较采用t检验或χ^2检验。**结果** 标准剂量组患者ADP诱导的IPA高于低剂量替格瑞洛组患者[(83.4±2.5)% *vs* (67.3±4.7)%,$P=0.043$],但2组IPA<50%患者比例差异无统计学意义[13.5%(7/52) *vs* 5.2%(5/96),$P=0.219$]。2组患者12个月MACCE发生率差异无统计学意义[19.2%(10/52) *vs* 13.5(13/96),$P=0.476$]。低剂量替格瑞洛组大出血事件发生率显著低于标准剂量替格瑞洛组[9.6%(5/52)*vs* 24.0%(23/96), $P=0.033$]。**结论** 低剂量替格瑞洛与标准剂量替格瑞洛相比同样可发挥较好的抗血小板作用,且降低出血事件风险,可更好地平衡缺血与出血。

【关键词】 急性冠脉综合征;替格瑞洛;主要不良心血管事件
【中图分类号】 R592;R541.4 【文献标志码】 A 【DOI】 10.11915/j.issn.1671-5403.2018.12.211

Efficacy of low-dose ticagrelor in the treatment of acute coronary syndrome in the elderly patients with chronic renal insufficiency

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【**Abstract**】 **Objective** To investigate the efficacy and safety of low-dose ticagrelor in the treatment of acute coronary syndrome (ACS) in the elderly patients with chronic renal insufficiency (CRI). **Methods** A total of 148 consecutive inpatients (aged ≥ 75 years) with ACS and CRI were enrolled in the study, who were admitted to the Department of Cardiology of the 986th Hospital of the PLA Air Force from October 2016 to February 2017. Patients were divided into low-dose ticagrelor group (LD group; 45 mg/once, twice/d; $n=52$) and standard-dose ticagrelor group (SD group; 90 mg/once, twice/d; $n=96$). Thromboelastography (TEG) was performed 3 days after oral administration. The 2 groups were compared in the inhibition rate of platelet aggregation (IPA) induced by ADP, and the incidence of major adverse cardiac and cerebrovascular events (MACCE) and hemorrhage events during a follow-up of 12 months. The data were analyzed using SPSS statistics 19.0. Student's t test or χ^2 test was performed for comparison. **Results** IPA induced by ADP in the SD group was higher than that in the LD group [(83.4±2.5)% *vs* (67.3±4.7)%, $P=0.043$], but there was no significant difference with IPA was fewer than 50% between 2 groups[13.5%(7/52) *vs* 5.2%(5/96),$P=0.219$]. No significant difference was found between the 2 groups in the incidence of MACCE at month 12 [19.2%(10/52) *vs*13.5(13/96),$P=0.476$]. The incidence of massive hemorrhage in the LD group was significantly lower than that in the SD group [9.6%(5/52) *vs* 24.0%(23/96), $P=0.033$]. **Conclusion** Low dose of ticagrelor can be as effective as standard dose in antiplatelet action, reducing the risk of bleeding events and maintaining a balance between ischemia and hemorrhage.

【**Key words**】 acute coronary syndrome; ticagrelor; major adverse cardiac and cerebrovascular events

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急性冠脉综合征(acute coronary syndrome, ACS)是发病率和死亡率较高的常见疾病,无论药物还是介入治疗,抗血小板治疗均是管理患者的基石。随着介入治疗发展和新型抗栓药物的临床应用,

收稿日期:2018-10-14;**修回日期**:2018-11-01
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ACS患者的整体预后得到了较大改善,但年龄仍是ACS患者预后不良的独立预测因素。老年ACS患者易发生复发性缺血事件,强效的抗血小板治疗可减少血栓事件发生和改善患者预后[1]。但矛盾的是老年ACS患者常合并慢性肾功能不全(chronic renal insufficiency,CRI),高龄及CRI是影响ACS患者预后的高危因素,应用抗血小药药物较低龄患者有更高的出血风险,因此老年ACS合并CRI患者抗血小板治疗的临床获益与出血风险需权衡。新型抗血小板药物替格瑞洛具有强效、迅速、可逆性抑制血小板聚集特点,其抗血小板的临床优势在现有的临床研究中逐步得到证实并获得多个指南推荐,其药代和药效优势使得ACS患者抗血小板治疗方案的优化成为可能[2-4],但出血是替格瑞洛临床常见的不良反应,也是ACS患者预后不良的危险因素。近年研究表明低剂量替格瑞洛与标准剂量替格瑞洛相比同样可发挥较好的抗血小板作用,且安全性优于标准剂量替格瑞洛[5],为此,本研究通过血栓弹力图(thrombelastography,TEG)监测下分析低剂量替格瑞洛对老年ACS合并CRI患者抗血小板治疗的疗效和安全性。

1 对象与方法

1.1 研究对象

连续入选2016年10月至2017年2月解放军空军第986医院心血管内科住院治疗的≥75岁老年ACS合并CRI患者148例,其中男性92例,女性56例,年龄(78.3±3.0)岁。根据患者服用替格瑞洛剂量不同分为低剂量替格瑞洛组(n=52)和标准剂量替格瑞洛组(n=96)。纳入标准:(1)临床诊断为ACS且病历资料完整;(2)估算肾小球滤过率(estimated glomerular filtration rate, eGFR)≤60 ml/(min·1.73 m^2);(3)签署知情同意书,同意入组并接受随访。排除标准:(1)严重肝功能不全,谷丙转氨酶≥正常上限2倍;(2)存在服用替格瑞洛禁忌证;(3)近1个月内参加过其他药物临床试验;(4)同时应用华法林、西洛他唑等其他抗血小板聚集药物;(5)各种血液系统出血性疾病。

1.2 方法

患者尽早给予阿司匹林和替格瑞洛片(阿斯利康制药有限公司,批准文号 H20120486),其他合并用药均按照指南给予个体化治疗。低剂量替格瑞洛组患者首次给90 mg负荷剂量,之后45 mg/次,2次/d;标准剂量替格瑞洛组患者首次给180 mg负荷剂量,之后90 mg/次,2次/d。口服替格瑞洛3 d后抽取静脉血行TEG检测,比较2组患者腺苷二磷酸(adenosine diphosphate,ADP)诱导的血小板聚集抑制率(inhibition of platelet aggregation,IPA)。

1.3 IPA检测

采用TEG凝血分析仪5000型(Haemoscope公司)及其配套检测试剂检测,具体方法为采集3 ml外周静脉血,室温放置30 min后,30转/min离心5 min制备富血小板血浆(platelet-rich plasma,PRP),吸取PRP后将剩余血样以160转/min离心8 min,制备贫血小板血浆(platelet-poor plasma,PPP);用自体PPP调整PRP的血小板计数为(200~250)×10^9/L,室温下备用。取PPP 300 μl置于比色管杯中作为空白对照,取PRP 300 μl置于比色管作为检测品,向检测样品中加入终浓度为20 μmol/L的ADP,诱导血小板聚集,通过分析仪得到血小板聚集动态曲线,曲线最高点即最大血小板聚集率(maximal aggregation rate,MAR)。IPA由计算机软件根据以下公式计算IPA(%)=(用药前MAR-用药后MAR)/用药前MAR×100%。ADP诱导的血小板抑制率通常要求IPA≥50%。

1.4 随访

随访12个月,比较2组患者主要不良心脑血管事件(major adverse cardiac and cerebrovascular events, MACCE)和大出血事件发生率。MACCE包括心源性死亡、再次心肌梗死、再次血运重建和脑卒中。大出血事件包括颅内、消化道等重要脏器及严重的鼻出血、齿龈出血、皮下出血。

1.5 统计学处理

采用SPSS 19.0统计软件对数据进行分析。计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验。计数资料以例数(百分率)表示,组间比较采用χ^2检验。以P<0.05为差异有统计学意义。

2 结 果

2.1 2组患者一般临床资料比较

2组患者年龄、性别、体质量指数、高血压、高脂血症、糖尿病、吸烟史、经皮冠状动脉介入(percutaneous coronary intervention,PCI)治疗患者比例等差异均无统计学意义(P>0.05;表1)。

2.2 2组患者服用药物3 d后ADP诱导的IPA比较

口服替格瑞洛3 d后抽取静脉血行TEG检测评价血小板功能,标准剂量组患者的IPA显著高于低剂量替格瑞洛组患者[(83.4±2.5)% *vs* (67.3±4.7)%,P=0.043],说明标准剂量抗血小板效果更强,但2组IPA<50%患者比例[13.5%(7/52) *vs* 5.2%

(5/96), P=0.219]差异无统计学意义。

2.3 2组患者治疗12个月MACCE及大出血事件发生率比较

2组患者心源性死亡、再次心肌梗死、再次血运重建、脑卒中及MACCE发生率差异均无统计学意义(P>0.05);低剂量替格瑞洛组患者较标准剂量替格瑞洛组患者大出血事件发生率[9.6%(5/52) *vs* 24.0%(23/96), P=0.033]显著降低,差异有统计学意义(表2)。

3 讨 论

ACS在老年人群中发病率较高且是患者主要死亡原因之一,文献报道>75岁老年人占所有因急性心肌梗死住院患者的1/3,占所有因心肌梗死导致死亡患者的2/3[6]。老年ACS患者常合并多种疾病,合并CRI的高龄患者体内凝血机制也会出现异常,因此抗血小板治疗后出血风险更高,抗血小板药物种类的选择及剂量面临极大的困难。出血事件是影响患者预后和导致住院病死率增加的重要危险因素之一,并且与出血事件的严重程度正相关,出血患者停用抗血小板药物后会再次导致缺血事件发生,从而增加患者死亡率,因此降低出血与缺血风险同样重要。

双重抗血小板治疗是ACS患者治疗的基石,用药时间应>12个月[7],现有指南对双联抗血小板治疗的剂量给出了推荐,在使用阿司匹林的基础上联合替格瑞洛90 mg, 2次/d,或氯吡格雷75 mg, 1次/d,这些推荐虽基于大型、多中心、双盲、随机临床试验,但这些研究中涉及的亚洲患者较少,且CRI是大多数临床试验的排除标准,因此关于老年ACS合并CRI患者抗血小板治疗的循证医学证据有限。著名PLATO研究[8]中关于慢性肾脏疾病患者的亚组研究,接近1/2的患者(3237例)年龄>75岁,并且基线资料分析表明年龄是这类患者出血风险增加的重要因素。PEGASUS-TIMI研究纳入21 000例患者,患者至少有1项高危因素(年龄≥65岁、2次心肌梗死病史、糖尿病、冠脉多支血管病变、肾功能不全)。随机给予替格瑞洛90 mg,2次/d;替格瑞洛60 mg,2次/d或安慰剂治疗,结果表明,替格瑞洛90 mg、2次/d组,或替格瑞洛6 mg、2次/d组,相比

表1 2组患者一般临床资料比较

Table 1 Comparison of baseline data between two groups

Item	Low-dose ticagrelor group (n=52)	Standard-dose ticagrelor group (n=96)	t/χ^2	P value
Age(years, $\bar{x}\pm s$)	77.5±2.5	79.4±4.1	0.125	0.624
Male[n(%)]	35(67.3)	57 (59.4)	0.902	0.342
BMI[kg/m^2, $\bar{x}\pm s$]	20.2±3.9	23.1±2.7	3.141	0.091
Hypertension[n(%)]	17(32.7)	41(42.7)	1.420	0.233
Hypercholesterolaemia[n(%)]	19(36.5)	45(46.9)	1.468	0.226
Diabetes mellitus[n(%)]	9(17.3)	30(31.3)	3.378	0.066
History of smoking[n(%)]	8(15.4)	26(27.1)	2.609	0.106
NSTE-ACS[n(%)]	28(53.8)	40(41.7)	2.015	0.156
STEMI[n(%)]	24(46.2)	56(58.3)	2.015	0.156
PCI[n(%)]	34(65.4)	68(70.8)	0.467	0.494
LVEF(%, $\bar{x}\pm s$)	63.6±9.4	58.0±7.5	3.342	0.131
SCr(μmol/L, $\bar{x}\pm s$)	328.0±30.3	281.5±33.8	2.430	0.125
eGFR≤60ml/(min·1.73 m^2)[n(%)]	46(88.5)	82(85.4)	0.015	0.902

BMI: body mass index; NSTE-ACS: non-ST segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; SCr: serum creatinine; eGFR: estimated glomerular filtration rate

表2 2组患者治疗12个月MACCE及大出血事件发生率比较

Table 2 Comparison of the incidence of MACCE and haemorrhage events between two groups after 12 months treatment

Item	Low-dose ticagrelor group (n=52)	Standard-dose ticagrelor group (n=96)	χ^2	P value
MACCE	10(19.2)	13(13.5)	0.832	0.476
Cardiac death	1(1.9)	2(2.1)	0.004	1.000
MI	3(5.8)	2(2.1)	1.404	0.345
Coronary revascularization	4(7.7)	8(8.3)	0.019	1.000
Stroke	2(3.8)	1(1.0)	1.336	0.282
Hemorrhage events	5(9.6)	23(24.0)	4.523	0.033
Dyspnea	5(9.6)	11(11.5)	0.184	0.668

MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction

安慰剂组均能显著降低患者 MACCE 发生率[替格瑞洛(90 mg)组 *vs* 安慰剂组(*HR* = 0.85, 95% *CI* 0.75~0.96; *P* = 0.008);替格瑞洛(60 mg)组 *vs* 安慰剂组(*HR* = 0.84, 95% *CI* 0.74~0.95; *P* = 0.004)]。替格瑞洛(60 mg)组的大出血事件和不良反应(如呼吸困难)发生率更低,说明低剂量替格瑞洛有效抗血小板的同时降低了患者出血风险,低剂量替格瑞洛可能更适合 ACS 患者的长期抗血小板治疗[9,10]。相关亚洲人群的临床试验[11,12]已报道,即使降低一定程度的剂量,替格瑞洛的 IPA 仍优于氯吡格雷。Husted 等[13]研究结果表明替格瑞洛 50 mg、2 次/d 的 IPA 仍高于氯吡格雷 75 mg、1 次/d。Hiasa 等[14]纳入 139 例亚洲稳定的冠心病患者(<80 岁),均接受过 PCI 治疗或有过 ACS 病史,随机分为 3 组,分别给予替格瑞洛 45 mg,2 次/d ;替格瑞洛 90 mg,2 次/d;氯吡格雷 75 mg,1 次/d 治疗,结果表明,服用研究药物后第 28 天,替格瑞洛 45 mg、2 次/d 组 IPA 虽低于替格瑞洛 90 mg、2 次/d,但仍高于氯吡格雷组。考虑种族、体质量、饮食结构等因素,适合国人的替格瑞洛剂量需要进一步大样本量的研究。

本研究结果表明低剂量替格瑞洛与标准剂量替格瑞洛有同样的抗血小板聚集效果;在有效性方面,随访 12 个月后表明低剂量替格瑞洛组总 MACCE 发生率与标准剂量替格瑞洛组差异无统计学意义,但低剂量替格瑞洛组大出血事件发生率显著低于标准剂量替格瑞洛组[9.6%(5/52) *vs* 24.0%(23/96), *P* = 0.033],可能与替格瑞洛抑制血小板作用较强有关,减少用量可减少发生出血事件的风险,因此初步说明低剂量替格瑞洛同样可发挥较好的抗血小板作用,同时降低患者出血风险,可能更好地平衡了老年 ACS 合并 CRI 患者缺血与出血事件的风险。

综上所述,低剂量替格瑞洛可有效抗血小板聚集和降低大出血事件发生风险,同时不增加患者 MACCE 发生率,可更好地平衡老年 ACS 合并 CRI 患者缺血与出血事件风险,但仍需大型随机对照的临床研究证实。

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(编辑: 王彩霞)