临床研究

双倍氯吡格雷维持剂量与替格瑞洛对慢代谢型患者的临床效果

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【摘 要】 **目的** 探讨细胞色素P450基因超家族CYP2C19慢代谢型患者使用双倍氯吡格雷维持剂量与替格瑞洛对于经皮冠状动脉介入(PCI)术后主要不良心血管事件(MACEs)发生的影响。**方法** 选取2014年6月至2016年9月解放军总医院心血管内科行PCI且CYP基因检测结果为慢代谢型患者205例,随机数字表法分为氯吡格雷组103例和替格瑞洛组102例,氯吡格雷组患者给予双倍维持剂量150 mg/d,3个月后更改为75 mg/d。替格瑞洛组给予180 mg负荷剂量后90 mg 2次/d的维持剂量,所有患者双联抗血小板药物服用时间均为12个月,12个月后随访结果。采用SPSS 17.0统计软件对数据进行分析,组间比较采用独立样本t检验、秩和检验、χ^2检验或Fisher确切概率法。**结果** 2组患者年龄、性别、体质量指数(BMI)、血小板计数、估计肾小球滤过率(eGFR)、ST段抬高型心肌梗死(STEMI)、非ST段抬高型心肌梗死(Non-STEMI)、高血压、高脂血症和既往是否行PCI等差异无统计学意义($P>0.05$)。氯吡格雷组和替格瑞洛组球囊预扩张压力[(12.3±2.8) *vs* (11.4±1.7)mmHg]和支架展开压力[(12.4±2.5) *vs* (11.5±2.2)mmHg]差异有统计学意义($P<0.05$)。氯吡格雷组MACEs发生率较替格瑞洛组明显升高[14.6%(15/103) *vs* 5.9%(6/102)],差异具有统计学意义($P=0.040$)。**结论** 慢代谢型患者使用替格瑞洛较150 mg氯吡格雷维持剂量可能会取得更优的临床效果。

【关键词】 冠心病;氯吡格雷抵抗;替格瑞洛
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Clinical efficacy of ticagrelor *versus* double maintenance dose of clopidogrel in poor-metabolizing patients after percutaneous coronary intervention

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【**Abstract**】 **Objective** To compare the effects of ticagrelor *versus* double maintenance dose of clopidogrel in poor-metabolizing (PM) patients [with an abnormal variant of cytochrome P450 family 2 subfamily C member 19 (CYP2C19)] after percutaneous coronary intervention (PCI). **Methods** A total of 205 patients with verified PM by CYP gene test who underwent PCI in the cardiological department of Chinese PLA General Hospital from June 2014 to September 2016 were recruited in this study. They were randomly divided into clopidogrel group ($n=103$) and ticagrelor group ($n=102$). The patients of the clopidogrel group were given 150 mg/d clopidogre for 3 months and then 75 mg/d for the other 9 months. While those from the ticagrelor group were given a loading dosage of 180 mg ticagrelor, followed by a maintenance dosage of 90 mg, twice per day. All of the patients were given dual antiplatelet agents for 12 months, and the outcomes were analyzed after 12 months of follow-up. SPSS statistics 17.0 was used to perform the statistical analysis. Independent sample t test, rank-sum test, Chi-square test, or Fisher exact test was employed for comparison between groups. **Results** There were no significant differences between the 2 groups in age, sex, body mass index (BMI), platelet count, estimated glomerular filtration rate (eGFR), ratios of those suffering from ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (Non-STEMI), hypertension and hyperlipidemia, and previous intervention of PCI ($P>0.05$). But obvious differences were seen in balloon dilatation pressure [(12.3±2.8) *vs* (11.4±1.7)mmHg] and stent expansion pressure

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[(12.4 ± 2.5) *vs* (11.5 ± 2.2) mmHg] between the 2 groups ($P < 0.05$). What's more, the incidence rates of major adverse cardiovascular events (MACEs) was notably higher in the clopidogrel group than in the ticagrelor group [14.6% (15/103) *vs* 5.9% (6/102), $P = 0.040$]. **Conclusion** Ticagrelor is superior to maintenance dose of 150 mg clopidogrel in clinical outcomes for the PM patients

【Key words】 coronary heart disease; clopidogrel resistance; ticagrelor

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冠心病患者行经皮冠状动脉介入(percutaneous coronary intervention, PCI)术后使用双联抗血小板(阿司匹林+氯吡格雷)预防主要不良心血管事件(major adverse cadiovascular events, MACEs)的发生已成为一种经典方法[1]。人群对阿司匹林药物反应的差异较小,发生阿司匹林药物抵抗的概率较低[2]。然而,人群中约1/3冠心病患者存在氯吡格雷药物抵抗现象[3],造成人群对氯吡格雷药物存在抵抗的原因很多,主要是氯吡格雷药物代谢基因不同、是否为急性冠状动脉综合征、是否合并糖尿病等因素[1,4-6]。文献报道,与氯吡格雷药物代谢相关基因的研究热点有细胞色素P450基因超家族(cytochrome P450 proteins, CYP)、对氧磷酶1(paraoxonase 1, PON1)、人ATP结合盒转运体B1(human ATP binding cassette transporter B1, ABCB1)等基因[6-8]。其中*CYP*基因多态性与氯吡格雷药物抵抗相关性较强[1,9],*CYP2C19*基因野生型为CYP2C19*1,而CYP2C19*2或CYP2C19*3携带患者对氯吡格雷药物抵抗的发生率明显升高[4]。降低氯吡格雷药物抵抗的方法有增加氯吡格雷药物负荷剂量、维持剂量或更换为替格瑞洛等[10-12]。既往研究未明确何种方法的效果更优,本研究针对慢代谢型患者使用双倍氯吡格雷维持剂量与替格瑞洛两者间的效果进行探讨。

1 对象与方法

1.1 研究对象

选取2014年6月至2016年9月解放军总医院心血管内科行PCI且*CYP*基因检测结果为慢代谢型(CYP2C19*2/*2、CYP2C19*2/*3、CYP2C19*3/*3)患者205例[6],随机数字表法分为氯吡格雷组103例和替格瑞洛组102例。纳入标准:年龄大于18岁;行PCI且CYP2C19检测结果为慢代谢型患者。排除标准:对阿司匹林、氯吡格雷或替格瑞洛过敏患者;不能持续口服双联抗血小板药物达12个月者;同时服用华法林等抗凝药物患者;估计肾小球滤过率(estimated glomerular filtration rate, eGFR)<30 ml/(min·1.73m^2)的患者;预期寿命<1年患者。

1.2 基因检测

基因检测由解放军总医院药学实验室承担,方法为核酸芯片杂交法,检测设备为BE-2.0生物芯片识度仪、BR-526-24全自动杂交仪,由上海百傲科技有限公司生产。患者入院当天抽取静脉血3 ml,加入依地酸二钠(ethylenediaminetetraacetate, EDTA)抗凝,按照外周血细胞DNA提取试剂盒步骤说明提取DNA后,琼脂糖凝胶电泳检测目的条带。聚合酶链反应(polymerase chain reaction, PCR)仪扩增后,按照核酸芯片杂交试剂盒步骤说明应用DNA测序仪进行基因测序,分析患者*CYP2C19*基因型。

1.3 冠状动脉造影及PCI

经桡或股动脉入路,6F或7F动脉鞘经桡动脉时动脉鞘内给予维拉帕米1 mg,造影后对狭窄血管进行PCI,包括球囊扩张、支架置入、血栓抽吸等。术中采用比伐芦定或肝素抗凝。支架置入成功定义为残余管腔狭窄<25%,无内膜撕裂或夹层,PCI术后血流心肌梗死溶栓试验(thrombolysis in myocardial infarction, TIMI)评分3级[3]。

1.4 PCI术后用药

根据检测结果按照美国食品和药品管理局建议调整给药剂量[6]。氯吡格雷组患者给予硫酸氢氯吡格雷[赛诺菲(杭州)制药有限公司,国药准字H20056410]300 mg负荷剂量,双倍维持剂量150 mg/d,3个月后更改为75 mg/d;替格瑞洛组患者每天给予替格瑞洛(阿斯利康制药有限公司,国药准字J20130020)180 mg负荷剂量,90 mg维持剂量,2次/d,所有患者使用双联抗血小板药物时间均为12个月。并于12个月后进行电话随访。

1.5 比较指标

比较2组患者MACEs的发生。MACEs包括支架内血栓、脑卒中、靶血管再次血运重建、心源性死亡、再次发作胸痛、因胸痛再次入院治疗。支架内血栓:明确的支架内血栓,由冠状动脉造影确认。心源性死亡:由任何原因引起的因心脏导致的死亡,也包括未知原因死亡与PCI并发症相关死亡。脑卒中:任何原因引起的缺血性或出血性事件导致局部神经功能障碍,至少持续24 h。靶血管再次血运重建:靶

血管任何的再次介入或者搭桥治疗,其中靶血管包括病变血管的上游、下游和分支血管。再次发作胸痛:胸痛症状较术后明显加重,包括活动后、静息时以及胸痛时心电图改变的患者。因胸痛再次入院治疗:术后因胸痛再次入院治疗,不包括正常复查患者[13]。

1.6 统计学处理

采用SPSS 17.0统计软件对数据进行分析,计量资料用均数±标准差($\bar{x}\pm s$)表示,当符合正态分布和方差齐性时,采用独立样本t检验;不符合正态分布或方差不齐时,采用独立样本秩和检验。计数资料用百分率表示,组间比较采用χ^2检验或Fisher确切概率法。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者基线资料比较

2组患者年龄、性别、体质量指数(body mass index,BMI)、血小板计数、eGFR、ST段抬高型心肌梗死(ST-segment elevation myocardial infarction,STEMI)、非ST段抬高型心肌梗死(non-ST-segment elevation myocardial infarction,Non-STEMI)、高血压、高脂血症和既往是否行PCI等差异无统计学意义($P>0.05$;表1)。

2.1 2组患者PCI情况比较

2组患者左主干病变、左前降支病变、左回旋支病变、右冠状动脉病变、单支病变、双支病变、三支病变、置入支架、支架总长度、支架直径、球囊预扩张比例、球囊后扩张压力和球囊后扩张比例差异无统计学意义($P>0.05$)。球囊预扩张和支架展开压力差异有统计学意义($P<0.05$;表2)。

2.2 2组患者MACEs发生率比较

2组患者支架内血栓(stent thrombus, ST)、靶血管再次血运重建(target vessel revascularization, TVR)、再次发作胸痛(recurrent angina pectoris, RAP)、心源性死亡、因胸痛再次入院(hospitalization because of angina pectoris,PBAP)差异无统计学意义($P>0.05$)。氯吡格雷组MACEs发生率较替格瑞洛组明显升高[14.6%(15/103) *vs* 5.9%(6/102)],差异具有统计学意义($P=0.040$;表3)。

3 讨 论

冠心病患者中约1/3存在氯吡格雷药物抵抗,从而导致PCI术后MACEs发生率明显升高[14]。增加患者氯吡格雷药物抵抗的原因有很多,如糖尿病、急性冠脉综合征、不同药物代谢基因型等[5,8],在此主要针对氯吡格雷药物代谢基因CYP进行讨论。

氯吡格雷在肝脏需经过两步代谢才能转化为有活性的产物[4],CYP2C19在这个过程中发挥了主导作用[4]。*CYP2C19*基因的野生型为(CYP2C19*1),功能丧失的*CYP2C19*基因多态性(CYP2C19*2、CYP2C19*3)与较高的氯吡格雷药物抵抗发生率有关,进而增加了PCI术后MACEs的发生率。CYP2C19*2、CYP2C19*3基因型在不同种人群中的发生率存在差异,CYP2C19*2在亚洲人群的发生率约为30%,而高加索人群和非洲、美洲人群的发生率分别为13%和18%[4,15,16]。CYP2C19*3在东亚人群和高加索人群的发生率分别为(5%~10%)和0%[4,15,16]。东亚人群中氯吡格雷慢代谢型几乎

表1 2组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Clopidogrel group ($n=103$)	Ticagrelor group ($n=102$)	t/χ^2	P value
Age(years, $\bar{x}\pm s$)	61.6±11.4	59.8±12.2	1.065	0.288
Female[n(%)]	21(20.4)	20(19.6)	0.020	0.889
BMI(kg/m^2, $\bar{x}\pm s$)	25.8±3.3	25.8±3.4	0.782	0.913
Platelet count($\times10^9/L$, $\bar{x}\pm s$)	208.1±63.3	214.0±59.8	-0.691	0.490
eGFR[ml/(min·1.73 m^2), $\bar{x}\pm s$]	94.3±22.7	94.0±21.5	-0.102	0.919
Current smoking[n(%)]	12(11.7)	16(15.7)	0.708	0.400
Unstable angina[n(%)]	82(79.6)	75(73.5)	0.304	1.057
Non-STEMI[n(%)]	10(9.7)	11(10.8)	0.064	0.800
STEMI[n(%)]	11(10.7)	16(15.7)	1.123	0.289
HLP[n(%)]	29(28.2)	36(35.3)	1.206	0.272
DM[n(%)]	22(21.4)	25(24.5)	0.288	0.592
Hypertention[n(%)]	78(75.7)	66(64.7)	2.979	0.084
History of PCI[n(%)]	24(23.3)	16(15.7)	1.892	0.196

BMI: body mass index; eGFR: estimated glomerular filtration rate; Non-STEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; HLP: hyperlipidemia; DM: diabetes mellitus; PCI: percutaneous coronary intervention

表2 2组患者PCI情况比较

Table 2 Comparison of PCI procedures between two groups

Item	Clopidogrel group ($n=103$)	Ticagrelor group ($n=102$)	t/χ^2	P value
Diseased vessel[n(%)]				
Single vessel	43(41.7)	42(41.2)	0.008	0.930
Double vessels	33(32.1)	29(28.4)	0.649	0.574
Triple vessels	27(26.2)	31(30.4)	0.538	0.507
Location of target vessels[n(%)]				
LM	2(1.9)	2(2.0)	0.000	0.992
LAD	56(54.4)	66(64.7)	2.732	0.132
LCX	30(29.1)	38(37.3)	1.528	0.216
RCA	50(48.5)	35(34.3)	4.276	0.039
Implanted stents(n, $\bar{x}\pm s$)	1.8±1.0	1.9±1.3	−0.863	0.389
Stent length(mm, $\bar{x}\pm s$)	45.2±27.7	43.8±30.2	0.329	0.742
Stent diameter(mm, $\bar{x}\pm s$)	3.3±2.7	3.0±0.4	1.155	0.250
Pre-ballon dilation[n(%)]	97(94.2)	99(97.1)	1.035	0.314
Pre-ballon dilation pressure(mmHg, $\bar{x}\pm s$)	12.3±2.8	11.4±1.7	0.000	0.005
Stent expansion pressure(mmHg, $\bar{x}\pm s$)	12.4±2.5	11.5±2.2	0.074	0.006
Post-ballon dilation[n(%)]	87(84.5)	88(86.3)	0.134	0.714
Post-ballon dilation pressure(mmHg, $\bar{x}\pm s$)	16.3±2.7	15.7±2.1	0.018	0.077
Ballons(n, $\bar{x}\pm s$)	2.8±1.6	2.7±1.7	0.136	0.892

PCI: percutaneous coronary intervention; LM: left main stem; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery. 1 mmHg=0.133 kPa

表3 2 组患者MACEs发生率比较

Table 3 Comparison of MACEs incidence between two groups

[n(%)]

Item	Clopidogrel group ($n=103$)	Ticagrelor group ($n=102$)	χ^2	P value
ST	1(1.0)	0(0.0)	0.990	1.000
TVR	1(1.0)	1(1.0)	0.000	1.000
RAP	8(7.8)	4(3.9)	1.375	0.241
PBAP	4(3.9)	1(1.0)	1.806	0.178
Cardiac death	1(1.0)	0(0.0)	0.990	1.000
MACEs	15(14.6)	6(5.9)	4.200	0.040

MACEs: major adverse cadiovascular events; ST: stent thrombus; TVR: target vessel revascularization; RAP: recurrent angina pectoris; PBAP: hospitalization because of angina pectoris

100%是由这两种基因变异导致的[15]。氯吡格雷药物抵抗会增加PCI术后围手术期心肌梗死(perioperative myocardial infarction, PMI)的发生率,并明显增加MACEs的发生率[15]。数据显示,慢代谢性型患者PMI的发生率较快中代谢型患者明显升高,而快代谢型与中代谢型患者的PMI发生率差异无统计学意义[15]。降低氯吡格雷药物抵抗的方法有增加氯吡格雷剂量或更改药物等方法[10,12],本研究针对慢代谢性患者使用双倍氯吡格雷药物维持剂量或使用替格瑞洛的方法。结果提示,相比替格瑞洛组患者,双倍氯吡格雷组患者MACEs发生率明显升高,提示针对慢代谢型患者采用双倍维持剂量的方法效果较差。

虽然双倍氯吡格雷维持剂量可降低氯吡格雷药物抵抗的发生率,但其抗血小板效果仍无法与替格瑞洛相比[17]。研究提示,糖尿病患者往往伴随更高的氯吡格雷抵抗发生率,研究者曾经将糖尿病患者氯吡格雷的负荷剂量增加到600 mg,仍未能达到非糖尿病患者同样的抗血小板效果[5];也有研究者针对糖尿病患者将氯吡格雷维持剂量增加到150 mg,在60%的患者中仍存在氯吡格雷药物抵抗[18]。研究者针对CPY2C19进行了类似的研究,针对中代谢型、慢代谢性患者增加氯吡格雷维持剂量,结果提示,与中代谢型患者的抗血小板效果相比,慢代谢型患者明显较差[6,19]。结合本研究结果提示针对慢代谢型患者,使用替格瑞洛可能会取得更优的临床效果。本研究不足之处是样本量较少,观察时间较短,其有效性和安全性还有待大样本多中心临床研究进一步评价。

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