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论著

## 替格瑞洛、氯吡格雷对急性冠脉综合征患者 PCI 术后血小板聚集率、血流动力学及免疫功能的影响

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**摘要** 目的:探讨替格瑞洛、氯吡格雷对急性冠脉综合征(ACS)患者经皮冠状动脉介入治疗(PCI)术后血小板聚集率、血流动力学及免疫功能的影响。方法:选取本院心血管内科收治的124例ACS患者作为研究对象,随机分为观察组( $n=62$ )和对照组( $n=62$ ),观察组给予替格瑞洛治疗,对照组给予氯吡格雷治疗,观察比较两组患者治疗前后血小板聚集率、血流动力学指标、免疫功能指标变化情况和出血情况。结果:治疗后,两组患者血小板聚集率(PAV)均低于治疗前( $P<0.05$ ),且观察组明显低于对照组( $P<0.05$ );治疗后,两组患者全血黏度(BV)、血浆黏度(PV)均低于治疗前( $P<0.05$ ),观察组明显低于对照组( $P<0.05$ ),而收缩期血流速度峰值(SPV),舒张期血流速度峰值(DPV),冠脉血流储备(CFVR)均高于治疗前( $P<0.05$ ),且观察组明显高于对照组( $P<0.05$ );治疗后,两组患者CD3<sup>+</sup>、CD4<sup>+</sup>水平均高于治疗前( $P<0.05$ ),观察组明显高于对照组( $P<0.05$ ),而CD8<sup>+</sup>水平低于治疗前( $P<0.05$ ),观察组低于对照组( $P<0.05$ );两组患者总出血事件发生率比较差异无统计学意义( $P>0.05$ )。结论:替格瑞洛能有效抑制ACS患者PCI术后血小板聚集,改善血流动力学和免疫功能,安全性高。

**关键词** 急性冠脉综合征;替格瑞洛;氯吡格雷;血小板聚集率;血流动力学;免疫功能

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### The effects of Ticagrelor and Clopidogrel on platelet aggregation rate, hemodynamics and immunologic function in patients with acute coronary syndrome after PCI

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**Abstract** **Objective:** To investigate the effects of Ticagrelor and Clopidogrel on platelet aggregation rate, hemodynamics and immunologic function in patients with acute coronary syndrome(ACS) after percutaneous coronary intervention(PCI). **Methods:** One hundred and twenty-four patients with ACS were randomly divided into observation group( $n=62$ ) and control group ( $n=62$ ), the observation group was treated with Ticagrelor and the control group with Clopidogrel, and the platelet aggregation rate, hemodynamic index, immune function index and occurrence of Bleeding condition were observed and compared between the two groups before and after treatment. **Results:** After treatment, the platelet aggregation rate(PAV) of the two groups was lower than that before treatment ( $P<0.05$ ), and the observation group was significantly lower than the control group ( $P<0.05$ ); after treatment, the whole blood viscosity (BV) and plasma viscosity (PV) of the two groups were lower than those before treatment ( $P<0.05$ ), the observation group was significantly lower than the control group ( $P<0.05$ ), while the peak systolic velocity (SPV), peak diastolic velocity (DPV) and coronary flow velocity reserve (CFVR) were higher than those before treatment ( $P<0.05$ ), and the observation group was significantly higher than the control group ( $P<0.05$ ); after treatment, the levels of CD3<sup>+</sup> and CD4<sup>+</sup> in the two groups were higher than those before treatment ( $P<0.05$ ), the level of CD8<sup>+</sup> in the observation group was significantly higher than that in the control group ( $P<0.05$ ), and the level of CD8<sup>+</sup> in the observation group was lower than that before treatment ( $P<0.05$ ); there was no significant difference in the total incidence of bleeding events between the two groups ( $P>0.05$ ). **Conclusion:** Ticagrelor can effectively inhibit platelet aggregation after PCI in ACS patients, and improve hemodynamics and immunologic function with high safety.

**Key words** acute coronary syndrome; Ticagrelor; Clopidogrel; platelet aggregation rate; hemodynamics; immunologic function

急性冠脉综合征(acute coronary syndrome, ACS)是临床常见冠心病的一种严重类型,包括不稳定型心绞痛、急性ST段抬高性心肌梗死与急性非ST段抬高性心肌梗死3种类型,具有高发病率、高致死率、高致残率及高复发的特点,严重威胁患者身心

健康<sup>[1-2]</sup>。经皮冠状动脉介入治疗(PCI)是ACS重要治疗手段,但药物洗脱支架很大程度上增加支架内血栓风险<sup>[3]</sup>。氯吡格雷联合阿司匹林是临床用于PCI术后抗血小板基础治疗方案,但部分患者存在氯吡格雷抵抗,且呈剂量依赖性,个体差异较大<sup>[4]</sup>。替格瑞洛是新一代抗血小板药,无需肝脏代谢激活,其十几种代谢产物均有抗血小板作用,且起效快<sup>[5]</sup>。因此,本

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研究旨在替格瑞洛、氯吡格雷对 ACS 患者 PCI 术后血小板聚集率、血流动力学及免疫功能的影响。

## 1 资料与方法

**1.1 临床资料** 取 2016 年 6 月–2017 年 6 月本院心血管内科收治的 124 例 ACS 患者作为研究对象,随机分为观察组( $n=62$ )和对照组( $n=62$ ),观察组给与替格瑞洛治疗,对照组给与氯吡格雷治疗。纳入标准:(1)确诊为 ACS 患者,并经冠脉造影显示至少有 1 支冠脉主干或主要分支狭窄,接受 PCI 治疗者;(2)年龄 $>18$  岁;(3)患者对本研究有一定了解,自愿参与,并签署知情同意书;(4)经本院伦理委员会审核并批准;排除标准:(1)入组前 1 周有抗血小板药物和抗凝血药物服用史者;(2)ACS 为既往 PCI 并发症者;(3)对研究所用药物不耐受者;(4)近 3 个月内服用激素类药物或免疫增强剂类药物者;(5)心功能 III~IV 级,心律失常者,心源性休克以及合并有出血倾向的疾病;(6)合并严重肝、肾功能不全或肿瘤患者;(7)需服用强 CYP3A 抑制剂/诱导剂治疗者;(8)哺乳和妊娠期妇女。研究组男 35 例,女 27 例;年龄 47~76 岁,平均( $56.08\pm 4.76$ )岁;病变类型:不稳定型 40 例,非 ST 段抬高 13 例,ST 段抬高 9 例;对照组男 33 例,女 29 例;年龄 46~78 岁,平均( $57.41\pm 4.72$ )岁;病变类型:不稳定型 39 例,非 ST 段抬高 15 例,ST 段抬高 8 例,两组患者性别、年龄、病变类型等一般资料比较,差异无统计学意义( $P>0.05$ )。

**1.2 治疗方法** 所有患者入院后给予阿司匹林、低分子肝素、他汀类药物常规治疗,择期行 PCI 术。观察组:在常规治疗基础上术前给予替格瑞洛(商品名:倍林达,生产厂家:瑞典 AstraZeneca AB 公司,规格:90 mg/片,批准日期:20170721)负荷剂量 180 mg,术后 90 mg,2 次/d,服用 1 年;对照组:在常规治疗基础上术前给予氯吡格雷(商品名:波立维,生产厂家:赛诺菲(杭州)制药有限公司,规格:75 mg/片,批准日期:20150610)负荷剂量 300 mg,术后 75 mg,1 次/d,服用 1 年,术后随访 1 年,2018 年 6 月结束。

**1.3 观察指标** 术后 2 周观察相关指标,(1)记录

血小板聚集率(PAV),采用全自动血流变仪(型号 LBY-N6 compact,北京普利生仪器有限公司)测定 PAV;(2)观察血流动力学指标:采用全自动血流变仪检测全血黏度(BV)、血浆粘度(PV),采用彩色多普勒超声诊断仪(型号 DC-N2S,深圳市迈瑞生物医疗电子股份有限公司)监测收缩期血流速度峰值(SPV),舒张期血流速度峰值(DPV),冠脉血流储备(CFVR)变化情况;(3)观察免疫功能指标:流式细胞仪(FACSCanto II,美国 BD 公司)检测 CD3<sup>+</sup>、CD4<sup>+</sup>、CD8<sup>+</sup>水平变化;(4)观察两组患者出血事件发生情况,包括主要出血、次要出血及轻微出血情况。

**1.4 统计学分析** 采用统计软件 SPSS 19.0 进行数据处理,计量资料用描述,两组间比较采用  $t$  检验,计数资料及率采用  $\chi^2$  检验,当  $P<0.05$  时,差异有统计学意义。

## 2 结果

**2.1 两组患者血小板聚集率比较** 治疗前,两组患者 PAV 比较差异无统计学意义( $P>0.05$ );治疗后,两组患者 PAV 均低于治疗前( $P<0.05$ ),且观察组明显低于对照组( $P<0.05$ ),见表 1。

表 1 两组患者血小板聚集率比较( $\bar{x}\pm s$ ,%)

Tab 1 Comparison of platelet aggregation rate between two groups ( $\bar{x}\pm s$ , %)

组别	$n$	PAV	
		治疗前	治疗后
对照组	62	65.35 $\pm$ 7.62	41.67 $\pm$ 5.73*
观察组	62	66.58 $\pm$ 7.51	35.54 $\pm$ 5.49*
$t$		0.905	6.082
$P$		0.367	0.000

与同组治疗前比较,\* $P<0.05$

**2.2 两组患者血流动力学指标比较** 治疗前,两组患者 BV、PV、SPV、DPV、CFVR 比较差异无统计学意义( $P>0.05$ );治疗后,两组患者 BV、PV 均低于治疗前( $P<0.05$ ),观察组明显低于对照组( $P<0.05$ ),而 SPV、DPV、CFVR 均高于治疗前( $P<0.05$ ),且观察组明显高于对照组( $P<0.05$ ),见表 2。

表 2 两组患者 SPV、DPV、CFVR 比较( $\bar{x}\pm s$ )

Tab 2 Comparison of SPV, DPV and CFVR between two groups( $\bar{x}\pm s$ )

组别	$n$	BV/(mPs/s)		PV/(mPs/s)		SPV/(cm/s)		DPV/(cm/s)		CFVR	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照组	62	1.98 $\pm$ 0.06	1.83 $\pm$ 0.05*	8.62 $\pm$ 0.58	7.16 $\pm$ 0.54*	12.37 $\pm$ 1.54	14.18 $\pm$ 1.59*	24.41 $\pm$ 3.33	29.26 $\pm$ 3.28*	2.18 $\pm$ 0.31	2.91 $\pm$ 0.33*
观察组	62	1.97 $\pm$ 0.07	1.62 $\pm$ 0.06*	8.69 $\pm$ 0.63	6.61 $\pm$ 0.36*	12.33 $\pm$ 1.61	15.96 $\pm$ 1.88*	24.59 $\pm$ 3.51	34.17 $\pm$ 3.64*	2.13 $\pm$ 0.28	3.42 $\pm$ 0.35*
$t$		0.854	21.171	0.644	6.673	0.141	5.692	0.293	7.890	0.942	8.348
$P$		0.395	0.000	0.521	0.000	0.888	0.000	0.770	0.000	0.348	0.000

与同组治疗前比较,\* $P<0.05$

2.3 两组患者免疫功能指标比较 治疗前,两组患者 CD3<sup>+</sup>、CD4<sup>+</sup>、CD8<sup>+</sup>水平比较差异无统计学意义 ( $P>0.05$ );治疗后,两组患者 CD3<sup>+</sup>、CD4<sup>+</sup>水平均高于

治疗前( $P<0.05$ ),观察组明显高于对照组( $P<0.05$ ),而 CD8<sup>+</sup>水平低于治疗前( $P<0.05$ ),观察组低于对照组( $P<0.05$ ),见表 3。

表 3 两组患者 CD3<sup>+</sup>、CD4<sup>+</sup>、CD8<sup>+</sup>水平比较( $\bar{x}\pm s$ ,%)

Tab 3 Comparison of CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup> levels between two groups( $\bar{x}\pm s$ ,%)

组别	n	CD3 <sup>+</sup>		CD4 <sup>+</sup>		CD8 <sup>+</sup>	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照组	62	65.25±3.61	67.11±4.32*	34.76±3.08	37.13±4.82*	37.19±4.25	34.59±3.52*
观察组	62	65.50±3.82	68.63±4.07*	35.32±3.15	39.18±4.26*	36.21±4.35	33.31±3.50*
t		0.375	2.017	1.001	2.509	1.269	2.030
P		0.709	0.046	0.319	0.013	0.207	0.44

与同组治疗前比较,\* $P<0.05$

2.4 两组患者出血事件比较 观察组患者发生次要出血 1 例,出血事件总发生率为 1.16%,对照组患者发生主要出血 1 例,次要出血 3 例,轻微出血 2 例,出血事件总发生率为 9.68%,两组患者总出血事件发生率比较差异无统计学意义( $\chi^2=2.422$ , $P=0.120$ )。

### 3 讨论

ACS 基本病理生理变化是患者冠状动脉粥样硬化斑块破裂、血小板激活、血栓形成等,而改善患者心肌组织血液灌注,恢复心肌正常供血供氧功能为其治疗的目的<sup>[6]</sup>。近年来采用 PCI 治疗较大降低 ACS 死亡率,但 PCI 术后患者体内血小板激活及其他因素持续作用,造成患者术后易复发,因此 ACS 患者 PCI 术后选择有效抑制血小板凝聚药物成为治疗关键。

氯吡格雷为临床常用抗血小板凝集药物,其主要生物效应是通过阻断二磷酸腺苷(ADP)与其受体结合,从而发挥抗血小板激活、聚集、黏附等作用,氯吡格雷与阿司匹林联合是 ACS 患者 PCI 术后治疗传统方案,但氯吡格雷需经肝脏代谢后才能发挥作用,起效较慢,血小板功能恢复慢,而且个体差异较大,部分患者有氯吡格雷抵抗<sup>[7-8]</sup>。而替格瑞洛为新型抗血小板凝集药物,其能可逆性地与血小板膜内 P2Y<sub>12</sub>S 受体结合,抑制 ADP 介导的血小板活化、新血凝块的形成,从而达到抗血小板凝集,改善血液流动,减少血脂沉聚的目的,同时有研究证实替格瑞洛比氯吡格雷起效快、作用完全<sup>[9-10]</sup>。本研究结果显示,治疗后,两组患者血小板聚集率(PAV)均低于治疗前,且观察组明显低于对照组,这与李松森<sup>[11]</sup>研究结果基本相一致,提示替格瑞洛对 ACS 患者 PCI 术后抗血小板聚集率效果优于氯吡格雷。BV、PV 反应患者血液黏稠度,SPV、DPV 可直接反应冠脉血流速度,与冠脉直接呈负相关,而 CFVR 可反应冠脉再通程度,是冠脉血液循环状况重要衡量指

标<sup>[12-13]</sup>。通过血流动力学比较显示,治疗后两组患者 BV、PV 均低于治疗前,观察组明显低于对照组,而 SPV、DPV、CFVR 均高于治疗前,且观察组明显高于对照组,这与罗勇等<sup>[14-15]</sup>研究结果基本相似,提示替格瑞洛能较好改善 ACS 患者 PCI 术后血液流动,保障患者术后冠脉血流充足,减小血栓形成。进一步分析对免疫功能影响显示,治疗后,两组患者 CD3<sup>+</sup>、CD4<sup>+</sup>水平均高于治疗前,观察组明显高于对照组,而 CD8<sup>+</sup>水平低于治疗前,观察组低于对照组,提示替格瑞洛能提高 ACS 患者 PCI 术后免疫功能,增强免疫力。有研究报道发现替格瑞洛能通过抑制小鼠树突状细胞抗原递呈激活 T 细胞免疫炎症反应,调节免疫功能<sup>[16]</sup>。本研究中替格瑞洛可能起到相似作用,改善患者免疫功能。

综上所述,本研究通过研究替格瑞洛、氯吡格雷对 ACS 患者 PCI 术后血小板聚集率、血流动力学及免疫功能的影响结果显示,替格瑞洛能有效抑制 ACS 患者 PCI 术后血小板凝集,改善血流动力学和免疫功能,出血率低,安全性高。

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