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替格瑞洛与氯吡格雷对急性心肌梗死患者介入治疗后的心功能和炎症反应的影响 *

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摘要 目的：探讨替格瑞洛与氯吡格雷对急性心肌梗死患者介入治疗后的心功能和炎症反应的影响。**方法：**选取 2015 年 1 月-2018 年 1 月期间我院收治的行介入治疗的急性心肌梗死患者 300 例为研究对象。根据随机数字表法将患者分为替格瑞洛组(n=150)和氯吡格雷组(n=150)，其中替格瑞洛组给予阿司匹林、替格瑞洛治疗，氯吡格雷组给予阿司匹林、氯吡格雷治疗。比较两组患者治疗前后的左心室射血分数(LVEF)、左心室舒张末期内径(LVEDd)及白介素 -6(IL-6)、C 反应蛋白(CRP)、可溶性 CD40 配体(sCD40L)、肿瘤坏死因子 -α(TNF-α)水平，随访 3 个月，观察两组患者随访期间心血管不良事件的发生情况。**结果：**两组患者治疗后 LVEF 较治疗前升高，且替格瑞洛组高于氯吡格雷组，LVEDd 较治疗前降低，且替格瑞洛组低于氯吡格雷组(P<0.05)。两组患者治疗后 IL-6、CRP、sCD40L、TNF-α 均较治疗前升高，但替格瑞洛组低于氯吡格雷组(P<0.05)。替格瑞洛组随访期间心血管不良事件总发生率为 10.00%(15/150)，显著低于氯吡格雷组患者的 31.33%(47/150)，组间比较差异有统计学意义(P<0.05)。**结论：**相较于氯吡格雷而言，替格瑞洛治疗行介入治疗的急性心肌梗死患者效果满意，可显著改善心功能，降低炎症因子水平及心血管不良事件发生率。

关键词：替格瑞洛；氯吡格雷；急性；心肌梗死；介入治疗；心功能；炎症反应

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Effects of the Treatment of Cardiac Function and Inflammatory Response in Patients with Acute Myocardial Infarction after Interventional Therapy with the Combination of Ticagrelor and Clopidogrel*

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ABSTRACT Objective: To investigate the effects of the treatment of cardiac function and inflammatory response in patients with acute myocardial infarction after interventional therapy with the combination of ticagrelor and clopidogrel. **Methods:** a total of 300 patients with acute myocardial infarction who underwent interventional therapy in our hospital from January 2015 to January 2018 were selected as the subjects. The patients were randomly divided into ticagrelor group (n=150) and clopidogrel group (n=150) according to the table method, in which the ticagrelor group were treated with aspirin and ticagrelor, and the clopidogrel group was treated with aspirin and clopidogrel. The cardiac function index [left ventricular ejection fraction (LVEF), left ventricular end diastolic radius (LVEDd)], inflammatory factor index [interleukins -6(IL-6), C reactive protein(CRP), soluble CD40 ligand(sCD40L) and tumor necrosis factor-α (TNF-α)] were compared between the two groups. 3 months of follow-up, the occurrence of adverse cardiovascular events. **Results:** LVEF was higher after treatment than that before treatment in the two groups, and the ticagrelor group was higher than that of the clopidogrel group. The LVEDd was lower than that before treatment, and ticagrelor group was lower that of than the clopidogrel group (P<0.05). The IL-6, CRP, sCD40L and TNF-α of the two groups increased after treatment, but the ticagrelor group was lower than that of clopidogrel group (P<0.05). The total incidence of adverse cardiovascular events was 10.00% (15/150) during the follow-up period in the group of the ticagrelor group group, which was significantly lower than that of the patients in the clopidogrel group 31.33% (47/150), there was a significant difference between the groups (P<0.05). **Conclusion:** Compared with clopidogrel, the effect of di greold in patients with acute myocardial infarction is satisfactory. It can significantly improve the cardiac function, reduce the level of inflammatory factors and reduce the incidence of adverse cardiovascular events.

Key words: Ticagrelor; Clopidogrel; Acute myocardial infarction; Interventional therapy; Cardiac function; Inflammatory response

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前言

急性心肌梗死是冠状动脉急性、持续性缺氧缺血所引发的心肌坏死，临床上多表现为剧烈而持久的胸骨后疼痛，同时伴有血清心肌酶活性增高及进行性心电图变化，可并发心律失常、休克或心力衰竭，常危及生命[1-3]。经皮冠脉介入治疗是治疗急性心肌梗死的主要方法，其治疗效果已得到证实。然而仍有部分患者介入治疗后存在无复流现象，且支架植入亦会加重患者血管炎症反应[4,5]。氯吡格雷是急性心肌梗死患者介入治疗后的常用药物，可有效降低血栓及再狭窄的发生率，然而氯吡格雷吸收和代谢受体内不同生物酶系的影响，由于相关基因发生变异，一些患者可能出现“氯吡格雷抵抗”，难以达到预期的治疗效果[6,7]。替格瑞洛是新型的可逆性 P2Y12 受体拮抗剂，具有起效快、作用持久等特点[8,9]。目前临床有关上述两种药物治疗的疗效对比研究并不多见，鉴于此，本研究通过探讨替格瑞洛与氯吡格雷对急性心肌梗死患者介入治疗后的心功能和炎症反应的影响，以期为临床治疗提供数据支持，现作如下报道。

1 资料与方法

1.1 一般资料

选取 2015 年 1 月 -2018 年 1 月期间我院收治的行介入治疗的急性心肌梗死患者 300 例为研究对象。纳入标准：(1)所有患者均符合 2015 年版《急性 ST 段抬高型心肌梗死诊断及治疗指南》[10]中有关急性心肌梗死的相关诊断标准并确诊；(2)所有患者均行介入治疗；(3)持续胸痛时间超过 30 min，心电图检查 2 个相邻导联 ST 段抬高≥ 0.1 mv；(4)药物治疗效果不佳的 ST 段压低患者；(5)所有患者及其家属知情本研究并签署同意书。排除标准：(1)合并肝、肾等脏器功能障碍者；(2)伴有先天性心脏疾病者；(3)精神异常及智力障碍者；(4)纳入本次研究前服用过影响凝血功能药物者；(5) 合并其他恶性肿瘤疾病者；(6)妊娠及哺乳期妇女。根据随机数字表法将患者分为替格瑞洛组(n=150)和氯吡格雷组(n=150)，其中替格瑞洛组男 73 例，女 77 例，年龄 39-63 岁，平均(46.13± 3.46)岁；发病至入院时间 6-12 h，平均(9.46± 0.37)h；梗死部位：前壁 38 例、下壁 46 例、前间壁 27 例、右室 39 例；植入支架 1-2 个。氯吡格雷组男 71 例，女 79 例，年龄 38-61 岁，平均(45.95± 4.02)岁；发病至入院时间 5-12 h，平均(8.71± 0.49)h；梗死部位：前壁 36 例、下壁 47 例、前间壁 29 例、右室 38 例；植入支架 1~2 个。两组患者一般资料比较差异无统计学意义(P>0.05)，均衡可比，本次研究经我院伦理委员会批准同意。

1.2 治疗方法

两组患者入院后均给予常规对症治疗，包括叮嘱患者绝对卧床休息、吸氧、服用β 受体阻滞剂、舌下含服硝酸甘油镇痛、服用血管紧张素转换酶抑制剂进行降压处理，监测患者血压、心率及血氧饱和度等。在此基础上，氯吡格雷组入院后口服氯吡格雷片(赛诺菲(杭州)制药有限公司，国药准字：H20056410，规格：75 mg)600 mg，同时联合口服阿司匹林(北京曙光药业有限责任公司，国药准字：H11021029，规格：0.3 g)300 mg 治疗，术后给予阿司匹林 100 mg，1 次 /d，氯吡格雷 75 mg，1 次 /d，维持治疗 12 周。替格瑞洛组入院后口服阿司匹林 300 mg，替格瑞洛(AstraZeneca AB，国药准字：J20130020，规格：90 mg)180 mg，术后给予阿司匹林 100 mg，1 次 /d，替格瑞洛 90 mg，2 次 /d，维持治疗 12 周。

1.3 观察指标

于治疗前、治疗 12 周后(治疗后)采用美国 GE 公司生产的 GE vivid7 彩色多普勒超声心动图检测患者左心室射血分数(left ventricular ejection fraction，LVEF)、左心室舒张末期内径(left ventricular end diastolic dimension，LVEDd)。于治疗前后采集患者清晨空腹静脉血 4 mL，3000 r/min 离心 10 min，取上清液置于 -30℃ 冰箱中待测。采用酶联免疫吸附法检测患者血清白介素 -6（interleukin -6，IL-6）、C 反应蛋白（C reactive protein，CRP）、可溶性 CD40 配体(soluble CD40 ligand，sCD40L)、肿瘤坏死因子 -α(tumor necrosis factor-α，TNF-α)水平，试剂盒来源于德国罗氏公司。采用电话询问或者门诊复查等方式随访 3 个月，观察两组患者随访期间不良心血管事件发生情况，包括心绞痛复发、心力衰竭、轻中度出血、呼吸困难等。

1.4 统计学方法

采用 SPSS20.0 进行统计分析，计数资料以例数及率的形式表示，采用卡方检验，计量资料以均值± 标准差($\bar{x}$± s)的形式表示，采用 t 检验，P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者心功能指标比较

两组患者治疗前 LVEF、LVEDd 比较差异无统计学意义(P>0.05)；两组患者治疗后 LVEF 较治疗前升高，且替格瑞洛组高于氯吡格雷组，LVEDd 较治疗前降低，且替格瑞洛组低于氯吡格雷组(P<0.05)；详见表 1。

表 1 两组患者心功能指标比较($\bar{x}$± s)

Table 1 Comparison of cardiac function indexes in two groups of patients($\bar{x}$± s)

Groups	n	LVEF(%)		LVEDd(mm)	
		Before treatment	After treatment	Before treatment	After treatment
Di greold group	150	46.04± 3.52	53.79± 3.74*	48.26± 3.52	45.12± 4.17*
Clopidogrel group	150	46.17± 3.75	68.81± 3.63*	47.95± 3.63	39.81± 4.21*
t	-	0.310	35.295	0.751	10.975
P	-	0.757	0.000	0.453	0.000

Note: compared with before treatment, *P<0.05.

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2.2 两组患者炎症因子指标比较

两组患者治疗前 IL-6、CRP、sCD40L、TNF-α 比较差异无统计学意义（P>0.05）；两组患者治疗后 IL-6、CRP、sCD40L、TNF-α 均较治疗前升高，但替格瑞洛组低于氯吡格雷组，组间比较差异有统计学意义（P<0.05）；详见表 2。

表 2 两组患者炎症因子指标比较($\bar{x}\pm s$)

Table 2 Comparison of the index of inflammatory factors in the two groups($\bar{x}\pm s$)

Groups	n	IL-6(pg/ml)		CRP(mg/L)		sCD40L(ng/L)		TNF-α(pmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Di greold group	150	4.58± 0.63	7.93± 0.62*	6.14± 0.76	13.53± 1.71*	495.04± 10.52	573.79± 13.74*	7.16± 0.92	12.12± 1.17*
Clopidogrel group	150	4.52± 0.71	5.78± 0.79*	6.08± 0.65	8.84± 1.37*	494.49± 11.49	534.83± 12.66*	7.14± 0.87	8.98± 0.83*
t	-	0.774	26.221	0.735	26.215	0.432	25.540	0.193	26.809
P	-	0.439	0.000	0.463	0.000	0.666	0.000	0.847	0.000

Note: compared with before treatment, *P<0.05.

2.3 两组患者随访期间心血管不良事件发生情况

替格瑞洛组随访期间心血管不良事件总发生率为 10.00%（15/150），显著低于氯吡格雷组患者的 31.33%（47/150），组间比较差异有统计学意义（P<0.05）；详见表 3。

表 3 两组患者随访期间不良事件发生情况 例(%)

Table 3 The incidence of adverse events during the follow-up period in two groups of patients n(%)

Groups	n	Recur of angina pectoris	Heart failure	Mild and moderate hemorrhage	Dyspnea	Total incidence
Di greold group	150	14(9.33)	10(6.67)	9(6.00)	14(9.33)	47(31.33)
Clopidogrel group	150	5(3.33)	1(0.67)	3(2.00)	6(4.00)	15(10.00)
x^2	-					20.819
P	-					0.000

3 讨论

急性心肌梗死的治疗目标是尽快恢复心肌组织细胞的再灌注，避免其功能以及存活性的进一步损伤。经皮冠脉介入治疗是治疗急性心肌梗死最有效的方法，然而对富含血栓的冠脉行介入治疗势必会增加血栓脱落或者远端微循环栓塞的风险，导致无复流现象产生[11-13]。而强化抗凝治疗可能会有助于减少血栓栓塞以及无复流现象的发生。另外经皮冠脉介入治疗可引起局部血管内膜损伤及随后的一系列炎症反应，引发一定程度的心肌损伤，导致心室重构以及心功能降低[14,15]。阿司匹林联合氯吡格雷是治疗急性心肌梗死患者介入治疗后常用药物，氯吡格雷作为目前广泛应用于临床的 P2Y12 受体拮抗剂，具有广泛的抗炎效果[16,17]。然而氯吡格雷作为前体药物，须经过肝脏代谢才能被激活，而急性心肌梗死患者由于代谢功能受到一定程度的损伤，导致氯吡格雷起效慢，加之其药效作用时间较短，距离达到预期的治疗目标尚有一定的差距[18]。替格瑞洛为新型抗栓药物，可发挥良好的抗血小板作用，且其进入人体后，无需经过肝脏，起效更快，疗效稳定，因此受到越来越多临床工作者的重视[19-21]。

本研究结果表明，两组患者治疗后 LVEF 较治疗前升高，且替格瑞洛组高于氯吡格雷组，LVEDd 较治疗前降低，且替格瑞洛组低于氯吡格雷组，提示相较于使用氯吡格雷而言，急性心肌梗死患者介入治疗后使用替格瑞洛治疗，心功能改善效果更明显。这主要是由于替格瑞洛进入人体后，迅速起效，生物活性不需依赖于肝酶催化，可在短时间内发挥抗血小板聚集的作用，降低血小板聚集所导致的无复流现象，从而改善介入治疗后的心肌血流灌注，并减轻心肌细胞损伤，减轻术后左心室重构，改善心功能[22-24]。IL-6、TNF-α 均是常见的炎症细胞因子，具有广泛的生物学活性，可促进炎症细胞聚集，黏附于心肌细胞，促进新生内膜过度增生，加速血栓形成过程，增加支架内再狭窄的发生率[25,26]。CRP 是一种急性时相反应蛋白，可在 IL-6 的调控下加重机体炎性损伤[27]。sCD40L 是由膜结合形白细胞分化抗原 CD40L 水解而形成的三聚肽片段，正常人群机体循环中只能检测到少量 sCD40L，而当机体出现炎症反应后，其水平会急剧增加[28]。两组患者治疗后 IL-6、CRP、sCD40L、TNF-α 均较治疗前升高，但替格瑞洛组低于氯吡格雷组，提示替格瑞洛改善炎症反应效果更佳。由于球囊扩张和支架植入的机械挤压造成血管内膜损伤，诱导并加重炎症损伤，P2Y12 受体常分布在血小板膜、炎症因子细胞表面，而替格瑞洛、氯吡格雷作为 P2Y12 受体拮抗剂，替格瑞洛对于 P2Y12 受体的拮抗作用更为明显，发挥强大的抗血小板聚集以及抗炎作用[29,30]。替格瑞洛组随访期间心血管不良事件总发生率显著低于氯吡格雷组患者，表明替格瑞洛治疗行介入治疗的急性心肌梗死患者，可显著降低心血管不良事件发生率，安全性较好。

综上所述，急性心肌梗死患者介入治疗后使用替格瑞洛治疗，可有效改善患者心功能，减轻炎症反应，减少心血管不良事件发生的风险，具有一定的临床应用价值。

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