doi: 10.13241/j.cnki.pmb.2015.18.015

·临床研究·

替格瑞洛与氯吡格雷对急性冠脉综合征患者经皮冠脉动脉介入术后血小板抑制效果的比较 *

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摘要 目的:比较替格瑞洛与氯吡格雷对急性冠脉综合征(ACS)患者经皮冠脉动脉介入术(PCI)后血小板的抑制效果。**方法:**选择2014年3月至8月在我院经替格瑞洛联合阿司匹林治疗的ACS患者85例(替格瑞洛组),按性别、年龄2:1匹配原则随机抽取同一时间服用氯吡格雷联合阿司匹林治疗患者170例(氯吡格雷组)为研究对象,两组患者均行PCI治疗,并于服用抗血小板药物负荷剂量2天(PCI术后)进行血栓弹力图(TEG)检测,观察和比较两组患者经ADP途径及经AA途径的血小板抑制率。**结果:**氯吡格雷组和替格瑞洛组经ADP途径的血小板抑制率分别为(66.60± 25.57)%、(82.10± 18.87)%,两组比较差异有统计学意义(P<0.05)。氯吡格雷组ADP抑制率<50%患者占总人数的29.4%,替格瑞洛组ADP抑制率<50%的患者占总人数的10.6%,两组差异有统计学意义(P<0.05),氯吡格雷组ADP抑制率>75%者占总人数的41.8%;而替格瑞洛组ADP抑制率>75%的患者占总人数的69.4%,两组抑制率差异也存在统计学意义 (P<0.05)。氯吡格雷组和替格瑞洛组经AA途径的血小板抑制率分别为 (88.70± 23.89)%、(90.32± 18.09)%,两组比较差异无统计学意义(P>0.05)。**结论:**替格瑞洛对ACS患者PCI术后血小板的抑制作用优于氯吡格雷。

关键词:急性冠脉综合征;血小板抑制率;替格瑞洛;氯吡格雷

中图分类号:R541.4 **文献标识码:**A **文章编号:**1673-6273(2015)18-3462-04

Comparison of Ticagrelor with Clopidogrel in the Treatment of Patients with Acute Coronary Syndrome in Platelet Reactivity*

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ABSTRACT Objective: To compare the inhibitory effect of ticagrelor and clopidogrel on the platelet of patients with acute coronary syndrome(ACS) after percutaneous coronary artery intervention(PCI). **Methods:** 255 cases of patients with ACS admitted in our hospital from March 2014 to August 2014 were selected for this study, in which 85 cases were treated by ticagrelor and aspirin and the other 170 cases were treated by clopidogrel and aspirin respectively. All the patients were given PCI treatment, and the thrombelastography(TEG) were detected 2 days after PCI and oral administration of load dosage of antiplatelet drugs, the latelet inhibition ratio through ADP and AA pathway were observed and compared between the two groups. **Results:** Adenosine diphosphate (ADP)-induced platelet inhibition ratio in clopidogrel group was (66.60± 25.57)%, which was (82.10± 18.87)% in the ticagrelor group and significantly higher than that of the clopidogrel group (P<0.05). Arachidonic acid(AA)-induced platelet inhibition ratio were (88.70± 23.89)%, (90.32± 18.09)% in the clopidogrel group and the ticagrelor group. There was no significant difference in the AA -induced platelet inhibition ratio between two groups (P>0.05). The percentages of patients with ADP-induced platelet inhibition ratio<50% were 29.4% and 10.6% in the clopidogrel group and ticagrelor group, there were significant differences between two groups (P<0.05). The percentages of patients with ADP-induced platelet inhibition ratio>75% were 41.8% and 69.4% in the clopidogrel group and the ticagrelor group, respectively, and there were significant differences between the two groups (P<0.05). **Conclusions:** Ticagrelor had greater inhibitory effect on the patients with ACS after PCI than Clopidogrel.

Key words: Acute coronary syndrome; Platelet inhibition ratio; Ticagrelor; Clopidogrel

Chinese Library Classification(CLC): R541.4 Document Code: A

Article ID: 1673-6273(2015)18-3462-04

前言

阿司匹林和氯吡格雷联合应用是急性冠脉综合征(acute

* 基金项目:国家自然科学基金项目(81270309)

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(收稿日期:2014-11-18 接受日期:2014-12-10)

coronary syndrome,ACS) 和经皮冠状动脉介入治疗(percutaneous conronary intervention,PCI) 后的标准抗血小板治疗药物[1-3]。但 CREST 注册研究发现,阿司匹林或氯吡格雷等抗血小板药物对机体血小板功能的抑制作用越低,患者的预后相对越差[4],15%~48%的患者对氯吡格雷呈低反应[5-8]。替格瑞洛是一种新型抗血小板药物，是一种可逆的、直接作用于二磷酸腺苷(ADP)受体 P2Y12 抑制剂的口服制剂[9-11],可更好地抑制血小板功能,减少心血管事件的发生。研究表明血栓弹力图(TEG)检测可用于监测各种不同抗血小板药物对机体血小板功能的抑制作用[12],并根据药物对血小板抑制率情况适当调整药物。本研究旨在通过血栓弹力图观察和和比较替格瑞洛及氯吡格雷对 ACS 患者 PCI 术后血小板的抑制效果。

1 资料与方法

1.1 研究对象

选择 2014 年 3 月至 8 月在我院经替格瑞洛联合阿司匹林治疗的 ACS 患者 85 例(替格瑞洛组),同时按性别、年龄 2:1 匹配原则随机抽取同一时间服用氯吡格雷联合阿司匹林治疗的患者 170 例(氯吡格雷组)为研究对象。病例排除标准:(1)已知双联抗血小板治疗有禁忌症;(2)有活动性出血、出血体质、有出血倾向者以及血液疾病;(3) 凝血功能异常;(4) 血小板 <100×10^9/L;(5)贫血患者。

1.2 研究方法

两组患者均行 PCI 术,并于服用抗血小板药物负荷剂量 2 天(PCI 术后)进行血栓弹力图(TEG)检测,观察两组患者经 ADP 途径及经 AA 途径的血小板抑制率。具体方法：患者在 PCI 术前常规服用阿司匹林 600 mg、氯吡格雷 600 mg 或替格瑞洛 180 mg 负荷剂量,行 PCI 术,术后常规口服阿司匹林 100 mg 1/ 日,氯吡格雷 75 mg 1/ 日或替格瑞洛 90 mg 2/ 日。经皮冠状动脉支架植入术后 2 天采取静脉血各 3 mL，分别置入肝素钠抗凝采血管和枸橼酸钠抗凝采血管,采血后尽量 2 h 内完成血栓弹力图检测。应用进口 TEG 分析仪，分别以花生四烯酸(AA)和二磷酸腺苷(ADP)为激活物检测血小板抑制率。

1.3 统计学分析

所有数据使用 SPSS13.0 软件进行数据分析，计量资料以均数± 标准差表示,正态分布且方差齐性的数据资料采用两独立样本均数比较的 t 检验,非正态分布及方差齐性的资料采用两独立样本比较的秩和检验,计数资料间比较采用 X^2 检验,以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组患者一般临床资料的比较

如表 1 所示,两组患者的年龄、性别、体重指数、吸烟及血脂等指标比较均无明显差异(P>0.05),但氯吡格雷组高血压和糖尿病患者的比例显著高于替格瑞洛组(P<0.05),众多研究发现糖尿病及高血压是冠心病发生的重要危险因素[13],这两种因素可能影响抗血小板药物的作用。

表 1 两组患者一般临床资料的比较

Table 1 Comparison of the general clinical data between two groups

General situation	Ticagrelor group(n=85)	Clopidogre group (n=170)	P-value
Age(years)	60.83± 9.71	62.71± 11.40	0.052
M/F(n/n)	65/20	130/40	1.000
Body mass index (kg/m^2)	25.73± 3.34	25.37± 3.01	0.500
Smoking(n,%)	45(52.9)	92(54.1)	0.859
Hypertension(n,%)	41(48.2)	112(65.9)	0.007
Hyperlipidemia(n,%0	32(37.6)	67(39.4)	0.785
Diabetes(n,%)	12(14.1)	62(36.5)	0.001

Note: M: men, F: female.

2.2 两组患者经 ADP 途径及经 AA 途径的血小板抑制率比较

(1) 氯吡格雷组经 ADP 途径的血小板抑制率为 (66.60± 25.57)%，而替格瑞洛组经 ADP 途径的血小板抑制率增至 (82.10± 18.87)%,明显高于氯吡格雷组,两组差异有统计学意义 (P<0.05)。(2) 氯吡格雷组经 AA 途径的血小板抑制率为 (88.70± 23.89)%，替格瑞洛组经 AA 途径的血小板抑制率为 (90.32± 18.09),替格瑞洛组较氯吡格雷组有所增高,但两组比较差异无统计学意义(P>0.05)。(3)氯吡格雷组经 ADP 途径的血小板抑制率 <50%者 50 例,占总人数的 29.4%,而替格瑞洛组经 ADP 途径的血小板抑制率 <50%者 9 例，占总人数的 10.6%，血小板抑制率 <50%的两组差异有统计学意义(P<0.05)，其中氯吡格雷组有 47 例患者因 ADP 抑制率不达标或因冠脉病变程度较重将氯吡格雷改为替格瑞洛或西洛他唑或氯吡格雷剂量加倍。氯吡格雷组 ADP 抑制率 >75%者 71 例,占总数的 41.8%,替格瑞洛组 ADP 抑制率 >75%者 59 例,占总人数的 69.4%，两组血小板抑制率 >75%的患者比例比较差异有统计学意义(P<0.05)。见表 2。

3 讨论

抗血小板药物是治疗 ACS 患者的基石[14,15]。但是氯吡格雷联合阿司匹林的抗血小板治疗存在很大的局限性[16],主要是前体药物转化为活性代谢产物缓慢且多变,血小板抑制作用不大且具有变异性[17,18],在反应差的患者中,患者主要终点事件发生率明显增高[19]。目前,冠心病患者对阿司匹林和氯吡格雷等抗

表 2 两组患者经 ADP 途径及经 AA 途径的血小板抑制率的比较

Table 2 Comparison of the platelet inhibition ratio through ADP and AA pathway between two groups

Platelet inhibition ratio	Ticagrelor group	Clopidogre group
AA IR(%)	90.32± 18.09	88.70± 23.89
ADP IR(%)	52.10± 18.87	66.60± 25.57*
ADP IR(0%~30%)	1(1.2)	14(8.2)
ADP IR(30%~50%)	8(9.4)	36(21.2)
ADP IR(50%~75%)	17(20)	49(28.8)
ADP IR(75%~100%)	59(69.4)	71(41.8)*

Note: *Ticagrelor group compared with ticagrelor group, P<0.05, IR: inhibition ratio.

血小板药物的反应性已经引起医疗界越来越多的重视及关注。替格瑞洛是一种新型的抗血小板药物,具有可逆性,可直接与受体结合且方便服用,比氯吡格雷具有更快、更强和更稳定的 P2Y12 抑制作用。PLATO 研究表明在 ACS 患者中,与氯吡格雷相比,抗血小板新型药物替格瑞洛更能降低主要终点事件的发生率(9.8% vs 11.7%),并且不增加严重出血的发生率[20]。因此,新型抗血小板药物替格瑞洛可能逐渐代替氯吡格雷成为冠心病患者抗栓治疗的首要选择。

TEG 通过对抽血样品在血块形成到收缩各阶段的特性进行评估,同时也可以对凝血因子、纤维蛋白原、血小板活性及纤溶过程进行评价，可以通过 AA 和 ADP 两种诱导剂诱导的血小板聚集在凝血过程中起的作用,评价患者对阿司匹林和氯吡格雷或替格瑞洛等抗血小板药物的反应性[21]。

本研究通过 TEG 对本院服用替格瑞洛联合阿司匹林及氯吡格雷联合阿司匹林双联抗血小板药物的 ACS 患者进行分析，结果显示服用替格瑞洛的患者经 ADP 途径的血小板抑制率明显高于服用氯吡格雷的患者,表明替格瑞洛比氯吡格雷的抗血小板功能更强。氯吡格雷组 ADP 抑制率 <50%的患者占总人数的 29.4%,ADP 抑制率 >75%的患者仅占总数的 41.8%,说明有很大一部分人对氯吡格雷呈低反应。而替格瑞洛组 ADP 抑制率 <50%的患者占总数的 10.6%,ADP 抑制率 >75%的患者占总数的 69.4%，虽然大部分患者对替格瑞洛反应良好,但仍有 10.6%的患者存在替格瑞洛低反应。在入选患者中,氯吡格雷组高血压及糖尿病患者明显多于替格瑞洛组,鉴于高血压和糖尿病是冠心病发生的危险因素,在一定的程度上可影响血小板功能,这也可能是氯吡格雷组血小板抑制率低于替格瑞洛组的原因之一。此外,服用替格瑞洛的 ACS 患者经 AA 途径的血小板抑制率仅略高于服用氯吡格雷的 ACS 患者，这可能与大部分患者对 AA 抑制率较高、个体间差异性及样本量较小有关，也不能排除替格瑞洛可以提高 AA 途径的血小板抑制率,但若要证实此作用仍需进一步大样本的深入研究。

因此,抗血小板药物治疗 ACS 患者应注重个体化,控制各方面危险因素,监测血小板功能并结合患者临床症状随时调整用药,在达到抗栓目的同时防止出血事件的发生。血栓与出血事件在冠心病患者治疗中是对矛盾体,要想达到最好治疗仍需要医师们积累更多临床经验及进一步的研究探索。

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