·临床研究·

替格瑞洛治疗非ST段抬高型急性冠脉综合征合并慢性阻塞性肺疾病患者的效果

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【摘 要】 目的 探讨替格瑞洛对非ST段抬高型急性冠脉综合征(NSTE-ACS)合并慢性阻塞性肺疾病(COPD)患者的疗效和安全性。**方法** 回顾性分析2018年1月至11月陕西省第四人民医院心血管内科NSTE-ACS合并COPD患者194例,根据使用抗血小板药物情况分为替格瑞洛组96例和氯吡格雷组98例。患者选择性行经皮冠状动脉介入(PCI)术,替格瑞洛组患者术前给予负荷剂量180 mg,术后和未手术给予90 mg,2次/d,氯吡格雷组患者术前给予负荷剂量300 mg,术后和未手术给予75 mg,2次/d,服药1个月后比较呼吸困难临床症状和改良版英国医学研究会呼吸困难量表(mMRC)评分,肺功能指标第1秒用力呼气容积(FEV1)、用力肺活量(FVC)、FEV1占预计值百分比(FEV1% pred)和FEV1/FVC。随访6个月后比较2组患者主要不良心脑血管事件(MACCE)和出血事件发生率。应用SPSS 22.0统计软件对数据进行分析。根据数据类型采用t检验或χ^2检验进行组间比较。**结果** 2组患者年龄、性别、体质量指数、高血压、糖尿病、高脂血症、不稳定性心绞痛、行PCI术比例等差异无统计学意义($P>0.05$)。服药1个月后替格瑞洛组相比氯吡格雷组患者呼吸困难临床症状评分[(2.2±0.6)和(1.4±0.8)分]、mMRC评分[(3.4±0.5)和(2.9±0.9)分]、FEV1/FVC[(75.7±4.6)%和(71.0±9.2)%]和FEV1% pred[(69.1±6.6)%和(67.6±5.9)%]差异无统计学意义($P>0.05$)。随访6个月后替格瑞洛组相比氯吡格雷组患者MACCE发生率[5.2%(5/96)和12.2%(12/98),$P=0.043$]显著降低,且出血事件发生率[19.8%(19/96)和10.2%(10/98),$P=0.061$]差异无统计学意义。**结论** 替格瑞洛不影响NSTE-ACS合并COPD患者肺通气功能,可有效降低短期MACCE发生风险,且出血事件发生率不增高。

【关键词】 急性冠脉综合征;肺疾病,慢性阻塞性;替格瑞洛
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Efficacy of ticagrelor in treatment of non-ST-segment elevation acute coronary syndrome patients accompanied with chronic obstructive pulmonary disease

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【Abstract】 Objective To investigate the efficacy and safety of ticagrelor in the treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients accompanied with obstructive pulmonary disease (COPD). **Methods** A retrospective analysis was made on 194 cases of NSTE-ACS combined with COPD from January to November 2018 in the Department of Cardiology of the Fourth People's Hospital of Shaanxi Province. According to the usage of antiplatelet drugs, they were divided into ticagrelor group ($n=96$) and clopidogrel group ($n=98$). All of them underwent elective percutaneous coronary intervention (PCI). The patients of the ticagrelor group were given at a loading dose of 180 mg preoperatively, and at 90 mg, twice a day post-operatively or to those non-operative patients. While, those of clopidogrel group were given 300 mg preoperatively, 75 mg, twice a day post-operatively, and 75 mg to the non-operative patients. In 1 month after administration, improvement of dyspnea, score of British Medical Research Council Scale (mMRC), forced expiratory volume in one second (FEV1), forced vital capacity (FVC), percentage of FEV1 to the predicted value (FEV1% pred) and FEV1/FVC were evaluated and compared between the 2 groups. The incidence of major adverse cardio-cerebrovascular events (MACCE) and bleeding events were also compared after 6 months of follow-up. SPSS statistics 22.0 was used for data analysis. Student's t test or Chi-square test was applied to make comparison between 2 groups according to the different data types. **Results** There were no significant differences in age, gender, body mass index, hypertension, diabetes, hyperlipidemia,

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unstable angina pectoris and proportion of patients undergoing PCI between the 2 groups ($P>0.05$). One month later, no significant differences were found in the score of clinical dyspnea symptoms (2.2±0.6 *vs* 1.4±0.8), mMRC score (3.4±0.5 *vs* 2.9±0.9), FEV1/FVC [(75.7±4.6)% *vs* (71.0±9.2)%] and FEV1% pred [(69.1±6.6)% *vs* (67.6±5.9)%] between the clopidogrel group and the ticagrelor group ($P>0.05$). After 6 months of follow-up, the incidence of MACCE was significantly lower in the ticagrelor group than the clopidogrel group [5.2%(5/96) *vs* 12.2%(12/98), $P=0.043$], but no difference was seen in that of bleeding events [19.8%(19/96) *vs* 10.2%(10/98), $P=0.061$]. **Conclusion** Ticagrelor does not affect the pulmonary ventilation function in patients with NSTE-ACS and COPD, and effectively reduces the risk of short-term MACCE, and has no effect on the incidence of bleeding events.

【Key words】 acute coronary syndrome; pulmonary disease, chronic obstructive; ticagrelor

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慢性阻塞性肺疾病(chronic obstructive pulmonary disease,COPD)可引起冠状动脉缺血和缺氧,严重时诱发冠状动脉痉挛或粥样硬化斑块破裂,继发血栓形成,可导致急性冠脉综合征(acute coronary syndrome,ACS)发生,临床上非 ST 段抬高型急性冠脉综合征(non-ST segment elevation acute coronary syndrome,NSTE-ACS)多见。阿司匹林联合 P2Y12 受体抑制剂的抗血小板策略是治疗 ACS 的基石,替格瑞洛抗血小板治疗快速、有效,可预防缺血事件发生,其有效性优于氯吡格雷,且不增加不良事件的发生,但增加药物相关呼吸困难的发生,因此替格瑞洛在 COPD 患者中的应用受到限制[1,2]。本研究初步探讨替格瑞洛对 NSTE-ACS 合并 COPD 患者的疗效和安全性。

1 对象与方法

1.1 研究对象

回顾性分析 2018 年 1 月至 11 月陕西省第四人民医院心血管内科 NSTE-ACS 合并 COPD 住院患者 194 例,根据使用抗血小板药物情况分为替格瑞洛组 96 例和氯吡格雷组 98 例。纳入标准:(1)临床诊断为 NSTE-ACS,诊断标准参照 2015 年欧洲心脏病学会发布的新版 NSTE-ACS 患者管理指南[3];(2)既往 COPD 病史或入院诊断为 COPD,COPD 诊断符合《中华医学会呼吸病分会 COPD 诊治指南(2013 年修订版)》标准[4];(3)愿意接受随访。排除标准:(1)服用药物禁忌证(如药物过敏、活动性出血史等);(2)需口服抗凝药治疗;(3)合并严重肝肾功能障碍;(4)临床资料不全;(5)治疗依从性差或无法完成随访。

1.2 方法

患者均给予阿司匹林肠溶片 100 mg,口服,1 次/d(拜耳先灵制药公司,国药准字 J20171021),根据病情及患者意愿选择是否行经皮冠状动脉介入治疗(percutaneous coronary intervention,PCI)术。替格瑞洛(阿斯利康制药有限公司,批准文号 H20120486)组患者术前给予负荷剂量 180 mg,术后和未手术均给予 90 mg,2 次/d;氯吡格雷(赛诺菲制药有限公司,批准文号 H20171237)组患者术前给予 300 mg 负荷剂量,术后和未手术均给予 75 mg,1 次/d。均服药 1 个月,记录 2 组患者治疗前和治疗 1 个月后呼吸困难临床症状和改良版英国医学研究会呼吸困难量表(modified British medical research council scale,mMRC)评分。呼吸困难临床症状评分标准:0 分,无呼吸困难症状;1 分:一般体力劳动时可感呼吸困难;2 分,轻度体力劳动时可感呼吸困难;3 分,平静状态时候可感呼吸困难[5]。mMRC 分值 0~4 分:0 分,除剧烈运动外一般不感到呼吸困难;1 分,平地急行时气短或上坡时气短;2 分,因气短平地行走时慢于同龄人或以自己的步速平地行走时必须停下来喘气;3 分,平地行走 100 m 或数分钟即有气短;4 分,因气短不能离开房间[6,7]。记录和比较第 1 秒用力呼气容积(forced expiratory volume in one second,FEV1)、用力肺活量(forced vital capacity,FVC)、FEV1 占预计值百分比(FEV1% pred)和 FEV1/FVC 等肺功能检查指标。

1.3 随访

随访 6 个月,比较 2 组患者主要不良心脑血管事件(major adverse cardiovascular and cerebrovascular events,MACCE)和出血事件发生情况。MACCE 定义为心源性死亡、非致死性心肌梗死、再次血运重建和脑卒中。心肌梗死溶栓治疗临床试验(thrombolysis in myocardial infarction,TIMI)出血分为(1)主要出血:颅内出血或临床可见出血(包括影像学诊断),伴血红蛋白浓度下降>50 g/L,包括致命性出血、伴心包填塞的心包内出血、出血导致的低血容量休克或严重低血压需升压药物或手术治疗;(2)小出血:临床可见出血(包括影像学诊断),伴血红蛋白浓度下降 3~5 g/dl;(3)轻微出血:临床可见出血(包括影像学诊断),血红蛋白浓度下降<3 g/dl[8]。

1.4 统计学处理

应用SPSS 22.0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,组间比较采用t检验。计数资料用例数(百分率)表示,组间比较用χ^2检验。$P<0.05$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)、高血压、糖尿病、高脂血症、不稳定性心绞痛、行PCI术比例等差异无统计学意义,具有可比性($P>0.05$;表1)。

2.2 2组患者治疗前和治疗1个月后肺功能指标水平比较

2组患者口服药物1个月后相比治疗前呼吸困难临床症状评分、mMRC评分、FEV1/FVC和FEV1% pred差异均无统计学意义($P>0.05$)。2组患者治疗前和口服药物1个月后呼吸困难临床症状评分、mMRC评分、FEV1/FVC和FEV1% pred组间差异也无统计学意义($P>0.05$;表2)。

2.3 2组患者MACCE和出血事件发生率比较

治疗6个月后,替格瑞洛组相比氯吡格雷组患者MACCE发生率降低,差异具有统计学意义($P<0.05$)。2组患者出血事件发生率差异无统计学意义($P>0.05$;表3)。

表1 2组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Ticagrelor group ($n=96$)	Clopidogrel group ($n=98$)	t/χ^2	P value
Age(years, $\bar{x}\pm s$)	63.8±11.0	66.4±10.1	0.502	0.543
Male[n(%)]	51(53.1)	62(63.3)	1.580	0.209
Hypertension[n(%)]	47(49.0)	59(60.2)	1.989	0.158
Hypercholesterolaemia[n(%]	52(54.2)	41(41.8)	3.405	0.065
Diabetes mellitus[n(%)]	29(30.2)	35(35.7)	0.511	0.474
History of smoking[n(%)]	27(28.1)	39(39.8)	2.594	0.107
BMI(kg/m^2, $\bar{x}\pm s$)	24.6±0.4	25.1±0.8	0.992	0.327
UA[n(%)]	81(84.4)	87(88.8)	0.276	0.600
PCI[n(%)]	92(95.8)	90(91.8)	2.513	0.114
SCr(μmol/L, $\bar{x}\pm s$)	95.4±18.6	89.5±10.2	2.018	0.164
BNP(U/L, $\bar{x}\pm s$)	493.5±78.4	438.0±92.4	1.980	0.210
LVEF(%, $\bar{x}\pm s$)	56.5±7.4	53.0±2.5	0.036	0.711
Number of diseased vessels(n, $\bar{x}\pm s$)	2.0±1.5	1.7±0.9	0.610	0.618
Number of implanted stents(n, $\bar{x}\pm s$)	2.5±1.8	1.8±1.5	3.121	0.081

BMI: body mass index; UA: unstable angina; PCI: percutaneous coronary intervention; SCr: serum creatinine; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction.

表2 2组患者呼吸困难评分和肺功能指标比较

Table 2 Comparison of dyspnea score and pulmonary function indicators between two groups ($\bar{x}\pm s$)

Group	n	Symptom of dyspnea (score)		mMRC (score)		FEV1/FVC(%)		FEV1% pred(%)	
		Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Ticagrelor	96	1.8±0.9	2.2±0.6	2.7±0.3	3.4±0.5	72.3±3.1	75.7±4.6	62.6±4.3	69.1±6.6
Clopidogrel	98	1.6±1.0	1.4±0.8	2.5±0.6	2.9±0.9	68.6±4.7	71.0±9.2	57.9±2.5	67.6±5.9

mMRC: modified British Medical Research Council Scale; FEV1: forced expiratory volume in one second; FVC: forced expiratory volume.

表3 2组患者MACCE和出血事件发生率比较

Table 3 Comparison of the incidence of MACCE and bleeding events between two groups [n(%)]

Group	n	MACCE	Cardiac death	MI	Coronary revascularization	Stroke	Bleeding events
Ticagrelor	96	5(5.2)	0(0.0)	2(2.1)	3(3.1)	0(0.0)	19(19.8)
Clopidogrel	98	12(12.2)	0(0.0)	4(4.1)	7(7.1)	1(1.0)	10(10.2)
χ^2		4.091	0.985	0.646	1.601	0.985	3.506
P value		0.043	1.000	0.683	0.331	1.000	0.061

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

3 讨 论

COPD患者因高龄、吸烟及全身炎症系统激活等因素,ACS发生率显著升高[9-11]。斑块破裂诱发急性血栓形成是ACS发病的病理生理基础,抗血栓形成是治疗基石,氯吡格雷与替格瑞洛均是常用的强化抗血小板治疗药物,但研究显示氯吡格雷抗血小板作用偏弱,易受肝内细胞色素P450酶激活、P2Y12受体不可逆结合及CYP2C19基因多态性等因素影响,且>15%患者药物敏感性低甚至无反应,氯吡格雷抵抗已成为ACS患者抗血栓治疗疗效欠佳的主要原因[12]。替格瑞洛为新型抗血小板药物,可强效、迅速、可逆性抑制血小板聚集,其抗血小板的临床优势在临床研究中逐步得到证实并获得多个指南推荐,其药效和药代优势使ACS患者优化抗血小板治疗成为可能[13-15],但替格瑞洛会增加呼吸困难等不良反应的发生,目前ACS合并COPD患者的临床应用经验不足。

国外研究显示替格瑞洛可增加呼吸困难发生率,发生率与用药剂量正相关,但绝大多数为轻中度呼吸困难,并不影响患者心肺功能,可用于ACS合并COPD患者[16,17]。国内学者周学敏等[18]把73例ACS合并COPD患者随机分为替格瑞洛组(38例)和氯吡格雷组(35例),1年后随访发现替格瑞洛组患者MACCE发生率(5.3%比25.7%,$P=0.04$)显著低于氯吡格雷组,出血事件发生率差异无统计学意义,表明阿司匹林联合替格瑞洛可减少ACS合并COPD患者发生MACCE的风险,且不增加出血事件的发生。刘曼华等[19]纳入140例ACS合并COPD患者,随机分为替格瑞洛组和氯吡格雷组,比较2组患者主要不良心血管事件发生率、全因病死率和出血事件发生率,结果发现替格瑞洛组患者主要不良心血管事件发生率显著低,而全因病死率和出血事件发生率差异无统计学意义。本研究比较了阿司匹林联合替格瑞洛和氯吡格雷用于NSTE-ACS合并COPD患者治疗前和口服药物1个月后呼吸困难临床症状评分、mMRC评分以及肺功能指标FEV1/FVC(%)和FEV1% pred,发现组间差异均无统计学意义,随访6个月结果显示替格瑞洛组患者MACCE发生率显著低于氯吡格雷组,出血事件发生率差异无统计学意义,与国内其他研究基本一致[20],分析其原因,可能与替格瑞洛可强效、迅速地抑制血小板聚集,减少靶血管缺血导致的不良事件有关,从而降低MACCE的发生率。

本研究初步表明替格瑞洛抗血小板治疗不影响NSTE-ACS合并COPD患者肺通气功能,并有效降低患者短期内发生MACCE的风险,且不增加出血事件的发生。本研究有以下局限性。(1)未对COPD患者严重程度分层,因而组间不平衡因素可能存在;(2)样本量偏小,非临床随机对照研究,因此对患者MACCE的预测有一定的偏倚;(3)本研究仅有6个月的随访数据,且随访观察指标简单有限,尚无远期随访资料进一步证实结论的可靠性。ACS合并COPD患者采用何种抗血小板联合方案可获得更佳临床受益,尚需随机对照研究进一步加以证实。

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