

· 临床研究 ·

## 茶碱缓释片治疗冠心病患者替格瑞洛相关呼吸困难的临床效果

张燕, 尚珊珊\*

(陕西省第四人民医院心血管内科, 西安 710043)

**【摘要】** 目的 观察茶碱缓释片治疗冠心病患者使用替格瑞洛后出现呼吸困难的临床效果。方法 入选2018年3月至2019年2月陕西省第四人民医院心血管内科服用替格瑞洛后引起呼吸困难但意识清楚、理解力正常的冠心病患者100例,随机数表法分为茶碱组和对照组,每组50例。2组患者均给予抗血小板聚集和他汀类药物以稳定斑块和改善心脏缺血,茶碱组患者在上述治疗基础上给予茶碱缓释片0.1g,对照组患者给予安慰剂维生素C 1g,口服,2次/d,服药1个月。比较2组患者血清腺苷水平、呼吸困难临床症状评分、应用改良版英国医学研究会呼吸困难量表(mMRC)评分、肺功能指标、呼吸衰竭和主要不良心脑血管事件(MACCE)发生率。采用SPSS 19.0统计软件对数据进行分析。结果 治疗后茶碱组相比对照组腺苷[(99.0±17.0)和(160.0±30.0) μg/L]、呼吸困难临床症状评分[(1.2±1.3)和(6.5±1.7)]、mMRC评分[(1.0±0.7)和(2.1±0.4)]、第1秒用力呼气容积(FEV1)占预计值百分比[(85.2±5.3)%和(76.9±7.0)%]、FEV1/用力肺活量[(89.3±3.9)%和(77.9±4.4)%]、呼吸衰竭发生率[2.0%(1/50)和18.8%(8/50)]显著下降,差异均具有统计学意义( $P<0.05$ )。2组患者MACCE发生率差异无统计学意义[6.0%(3/50)和10.0%(5/50),  $P=0.715$ ]。结论 茶碱缓释片可有效减轻替格瑞洛相关呼吸困难,改善患者通气功能,并且不影响替格瑞洛抗血小板聚集作用。

**【关键词】** 茶碱;呼吸困难;替格瑞洛

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## Clinical efficacy of theophylline sustained-release tablets in treatment of tigilillo-related dyspnea in patients with coronary heart disease

ZHANG Yan, SHANG Shan-Shan\*

(Department of Cardiology, the Fourth People's Hospital of Shaanxi Province, Xi'an 710043, China)

**【Abstract】 Objective** To observe the clinical efficacy of theophylline sustained-release tablets in treatment of dyspnea in coronary heart disease (CHD) patients after administration of ticagrelor. **Methods** A total of 100 CHD patients who experienced breathing difficulty but had clear consciousness and normal comprehension after taking ticagrelor in the Department of Cardiology of our hospital from March 2018 to February 2019 were enrolled in the study. They were randomly divided into theophylline group and control group, with 50 cases in each group. Both groups were given anti-platelet aggregation and statins to stabilize plaque and improve heart ischemia. Theophylline sustained-release tablets were given to the theophylline group on the basis of the above treatment, 0.1 g orally, vitamin C were given to the control group, 1 g orally, twice a day for 1 month. Serum adenosine levels, score of clinical symptoms of dyspnea, modified British Medical Research Association dyspnea scale (mMRC), pulmonary function indicators, respiratory failure and incidence of major adverse cardiovascular and cerebrovascular events (MACCE) were compared between the 2 groups. SPSS statistics 19.0 was used for data analysis. **Results** The theophylline group had significantly lower serum adenosine concentration [(99.0±17.0) vs (160.0±30.0) μg/L], score of clinical symptom of dyspnea [(1.2±1.3) vs (6.5±1.7)], mMRC score [(1.0±0.7) vs (2.1±0.4)], forced expiratory volume in 1 second (FEV1) as a percentage of prediction [(85.2±5.3)% vs (76.9±7.0)%], FEV1/forced vital capacity [(89.3±3.9)% vs (77.9±4.4)%], and incidence of respiratory failure [2.0%(1/50) vs 18.8%(8/50)] when compared with the control group ( $P<0.05$ ). There was no significant difference in the incidence of MACCE between the 2 groups [6.0%(3/50) vs 10.0%(5/50),  $P=0.715$ ]. **Conclusion** Theophylline tablets effectively alleviate the dyspnea caused by ticagrelor, improve the ventilatory function, and have no effect on antiplatelet aggregation induced by ticagrelor in the CHD patients.

**【Key words】** theophylline; dyspnea; ticagrelor

Corresponding author: SHANG Shan-Shan, E-mail: shangss520@163.com

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通信作者: 尚珊珊, E-mail: shangss520@163.com

随着生活水平提高和生活方式转变,冠心病发病率逐年上升且呈年轻化趋势,严重威胁人们的健康。阿司匹林联合 P2Y12 受体抑制剂的抗血小板策略已成为治疗冠心病的基石<sup>[1]</sup>。PLATO 研究证实替格瑞洛抗栓快速、有效,能更有效地预防缺血事件发生,且不增加总体严重出血风险,已成为首选的 P2Y12 受体抑制剂<sup>[2,3]</sup>。但随着替格瑞洛的广泛应用,与其相关的呼吸困难越来越受到临床医师的关注,替格瑞洛相关呼吸困难的发生率高,相关治疗方法少,停药后易导致患者临床获益减少。研究表明替格瑞洛相关呼吸困难的发生与体内腺苷水平升高有关<sup>[4]</sup>,可增加患者发生呼吸衰竭的风险。而茶碱缓释片能对抗腺苷等因素引起的呼吸道收缩,舒张支气管,且不良反应少,为此,本研究初步探讨了茶碱缓释片治疗替格瑞洛相关呼吸困难的临床效果。

## 1 对象与方法

### 1.1 研究对象

入选 2018 年 3 月至 2019 年 2 月陕西省第四人民医院心血管内科服用替格瑞洛后引起呼吸困难但意识清楚、理解力正常的冠心病患者 100 例,随机数表法分为茶碱组和对照组,每组 50 例。纳入标准:(1)呼吸困难发生在服用替格瑞洛后,既往无类似症状发生;(2)呼吸困难多在安静时发生,与患者活动、情绪变化等因素无关;(3)治疗后呼吸困难不能缓解的心绞痛和心功能不全;(4)肺功能、血氧饱和度或动脉血氧分压未见明显异常<sup>[5]</sup>。排除标准:(1)既往有支气管哮喘和慢性阻塞性肺疾病;(2)严重肝肾功能不全及心功能不全;(3)有抗血小板治疗禁忌;(4)对茶碱或黄嘌呤衍生物过敏;(5)治疗依从性差或无法完成随访。患者均签署知情同意书。

### 1.2 方法

2 组患者均给予抗血小板聚集和他汀类药物以稳定斑块和改善心脏缺血。茶碱组患者在上述治疗基础上给予茶碱缓释片(北京紫竹药业,国药准字 H1020150)0.1 g,口服,2 次/d,改善患者呼吸困难症状,对照组患者给予安慰剂维生素 C(华中药业股份有限公司,国药准字 H42020614)1 g,口服,2 次/d,共服药 1 个月。

### 1.3 检测指标

服药前和服药 1 个月后抽取静脉血检测血清腺苷水平,应用改良版英国医学研究会呼吸困难量表(modified British medical research council scale, mMRC)和呼吸困难临床症状评分对患者进行评分。mMRC 分值 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<sup>[6,7]</sup>。呼吸困难临床症状评分 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:平静状态时可感呼吸困难<sup>[8]</sup>。同时检查肺功能,记录患者第 1 秒用力呼气容积(forced expiratory volume in one second, FEV1)占预计值百分比(FEV1% pred)以及 FEV1 和用力肺活量(forced vital capacity, FVC)的比值。

### 1.4 随访

随访 1 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)发生率。MACCE 包括心源性死亡、非致死性心肌梗死、再次血运重建和脑卒中。

### 1.5 统计学处理

采用 SPSS 19.0 统计软件对数据进行分析。计量资料以均数±标准差( $\bar{x} \pm s$ )表示,组间比较采用 *t* 检验。计数资料以例数(百分率)表示,组间比较采用  $\chi^2$  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、高血压、糖尿病、高脂血症比例、血肌酐、脑钠肽(brain natriuretic peptide, BNP)、左心室射血分数(left ventricular ejection fraction, LVEF)及临床用药情况等差异均无统计学意义(*P* > 0.05; 表 1)。

### 2.2 2 组患者治疗前后肺功能和腺苷比较

2 组患者治疗前血清腺苷、呼吸困难临床症状评分、mMRC 评分、FEV1% pred 和 FEV1/FVC 差异无统计学意义(*P* > 0.05)。治疗后茶碱组相比对照组腺苷、呼吸困难临床症状、mMRC 评分显著降低,FEV1% pred 和 FEV1/FVC 显著升高,差异具有统计学意义(*P* < 0.05; 表 2)。

### 2.3 2 组患者随访结果比较

患者 1 个月后均成功随访,茶碱组相比对照组呼吸衰竭发生率显著降低,差异具有统计学意义(*P* < 0.05)。2 组患者 MACCE 发生率差异无统计学意义(*P* > 0.05; 表 3)。

### 2.4 茶碱组不良反应情况

茶碱组患者 2 例恶心、呕吐,1 例心悸,1 例头痛,不良反应发生率 8%(4/50),症状轻微,停药后不良反应消失,无急性尿潴留、失眠等严重不良反应发生。

表 1 2组患者基线资料比较

Table 1 Comparison of baseline data between two groups

(n=50)

Item	Theophylline group	Control group	t/χ <sup>2</sup>	P value
Age (years, $\bar{x}\pm s$ )	63.8±11.0	66.4±10.1	0.449	0.542
Male[n(%)]	30(60.0)	34(68.0)	0.694	0.405
Hypertension[n(%)]	24(48.0)	22(44.0)	0.161	0.688
Hypercholesterolaemia[n(%)]	12(24.0)	20(40.0)	2.941	0.086
Diabetes mellitus[n(%)]	14(28.0)	18(36.0)	0.735	0.391
History of smoking[n(%)]	14(28.0)	10(20.0)	0.877	0.349
Previous myocardial infarction[n(%)]	4(8.0)	8(16.0)	1.515	0.218
SCr(μmol/L, $\bar{x}\pm s$ )	95.4±18.6	89.5±10.2	1.922	0.164
BNP(U/L, $\bar{x}\pm s$ )	493.5±78.4	438.0±92.4	2.040	0.210
LVEF(% , $\bar{x}\pm s$ )	56.5±7.4	59.0±2.5	0.149	0.711
GRACE(score, $\bar{x}\pm s$ )	136.0±23.0	145.0±31.0	1.651	0.134
Aspirin[n(%)]	48(96.0)	50(100.0)	2.041	0.495
Statins[n(%)]	50(100.0)	49(98.0)	1.010	1.000
Beta blocker[n(%)]	40(80.0)	34(68.0)	1.871	0.171
ACEI/ARB[n(%)]	22(44.0)	26(52.0)	0.641	0.423
CCB[n(%)]	6(12.0)	12(24.0)	2.439	0.118

SCr: serum creatinine; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; GRACE: global registry of acute coronary events; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker.

表 2 2组患者治疗前后肺功能和腺苷水平比较

Table 2 Comparison of pulmonary function and adenosine level before and after treatment between two groups (n=50,  $\bar{x}\pm s$ )

Item	Theophylline group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Adenosine(μg/L)	91.0±23.0	99.0±17.0*#	88.0±27.0	160.0±30.0
Clinical symptom score of dyspnea(score)	5.7±1.6	1.2±1.3*#	5.0±1.4	6.5±1.7
mMRC(score)	2.3±0.4	1.0±0.7*#	2.3±0.7	2.1±0.4
FEV1%pred(%)	74.1±6.6	85.2±5.3*#	77.1±8.3	76.9±7.0
FEV1/FVC(%)	75.7±4.6	89.3±3.9*#	76.0±3.7	77.9±4.4

mMRC: modified British medical research council scale; FEV1: forced expiratory volume in one second; FVC: forced expiratory volume. Compared with before treatment, \*P<0.05; compared control group, #P<0.05.

表 3 2组患者呼吸衰竭和 MACCE 发生率比较

Table 3 Comparison of incidence of respiratory failure and MACCE between two groups

[n=50, n(%)]

Group	Respiratory	Cardiac	Myocardial	Coronary	Stroke
	failure	death	infarction	revascularization	
Theophylline	1(2.0)	0(0.0)	0(0.0)	2(4.0)	1(2.0)
Control	8(18.8)	1(2.0)	1(2.0)	3(6.0)	0(0.0)
χ <sup>2</sup>	5.983	1.010	1.010	0.211	1.010
P value	0.031	1.000	1.000	0.646	1.000

MACCE: major adverse cardiac and cerebrovascular events.

### 3 讨论

替格瑞洛具有强效、迅速、可逆性抑制血小板聚集特点,其抗血小板的临床优势获得多个指南推荐,但呼吸困难是其临床常见的不良反应,且容易误诊和误治。RESPOND 研究中呼吸困难发生率为 13%<sup>[9]</sup>。PLATO 研究显示约 13.8% 患者发生呼吸困难,有 5.9% 的患者因不能耐受呼吸困难而过早停止治疗,从而影响患者预后<sup>[10]</sup>。替格瑞洛引起呼吸困难机制尚不完全清楚。Bonello 等<sup>[11]</sup>检测了药

物治疗后急性冠状动脉综合征患者的腺苷水平,结果显示替格瑞洛组患者血浆腺苷水平明显高于氯吡格雷组。也有研究认为替格瑞洛可抑制体内红细胞膜上的平衡型核苷转运体,使红细胞对腺苷吸收降低,使得血液中腺苷水平升高,刺激肺迷走神经的 C 纤维,从而导致呼吸困难<sup>[12,13]</sup>。

茶碱可抑制磷酸二酯酶活性,增加细胞内环磷酸腺苷和环磷酸鸟苷的含量,减少血清腺苷的生成,起到松弛气管平滑肌和舒张支气管作用,改善患者通气功能,从而减轻呼吸困难症状和减少呼吸衰竭

的发生。国内王小东等<sup>[14]</sup>纳入181例替格瑞洛相关呼吸困难的冠心病患者,观察氨茶碱对患者呼吸困难的临床疗效,结果证实氨茶碱可减轻替格瑞洛相关呼吸困难症状和降低呼吸衰竭发生率。刘亚梅等<sup>[4]</sup>把服用替格瑞洛后出现呼吸困难的172例冠心病患者随机分为干预组和对照组,干预组给予多索茶碱片,对照组给予安慰剂,治疗后干预组呼吸困难缓解率明显高于对照组(93%和63%, $P < 0.05$ )。Wittfeldt等<sup>[15]</sup>纳入40名健康男性受试者,采用随机、双盲、安慰剂对照的研究方法,结果显示与安慰剂相比,替格瑞洛增加受试者血清腺苷浓度,患者输注茶碱后腺苷浓度下降且呼吸困难症状减轻。

本研究表明茶碱缓释片可对抗替格瑞洛导致的血清腺苷水平升高,改善呼吸困难症状和提高患者通气功能,减少呼吸衰竭的发生,进而减弱替格瑞洛相关呼吸困难的不良反应,提示茶碱缓释片可改善患者呼吸困难的状况,与国内外研究茶碱类改善替格瑞洛相关呼吸困难的结果相一致<sup>[4,14,15]</sup>。另外经过1个月的随访,2组患者MACCE发生率差异无统计学意义,说明茶碱缓释片治疗替格瑞洛相关呼吸困难安全,可缓解患者呼吸困难症状和恐慌心理,从而提高患者服用替格瑞洛的依从性,进一步保证了替格瑞洛抗血小板作用的发挥。

综上,茶碱缓释片有望成为替格瑞洛相关呼吸困难的临床新选择,但本文为小样本临床研究,且随访时间短,关于茶碱对替格瑞洛相关呼吸困难的临床疗效仍需大样本多中心的随机对照临床研究进一步证实。

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