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Original Article

Safety and efficacy of ticagrelor with emergency percutaneous coronary intervention in senile patients with ST-segment elevation myocardial infarction and dementia

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Abstract: Antiplatelet drug therapy is an important supportive measure for patients undergoing emergency percutaneous coronary intervention (PCI), to promote blood flow and reduce the risk of stent thrombosis. Ticagrelor is a new antiplatelet drug that offers some advantages over older drugs like clopidogrel in general ST-segment elevation myocardial infarction (STEMI) patients. However, its safety and efficacy in STEMI patients who also exhibit dementia and its underlying pathologies is unknown. Here, the application of ticagrelor was assessed in STEMI patients with dementia undergoing PCI. The study included 174 patients with dementia, ages 60 to 79 years, who were hospitalized due to STEMI from July 2014 to June 2015. All patients were treated by PCI. Before PCI, patients were randomly divided into two groups: one receiving ticagrelor and the other receiving clopidogrel to prevent cardiovascular thrombotic events. Patients were followed for 30 days to record cardiovascular events, bleeding, and other adverse reactions. Statistical analysis was performed using t-test, chi-square test and logistic regression analysis. The primary endpoint of vascular causes of death, stroke, and MI was less frequent in patients receiving ticagrelor than those receiving clopidogrel ($P<0.05$). The incidence of stent thrombosis was also lower in the ticagrelor group ($P<0.05$). However, some adverse events, i.e., upper gastrointestinal bleeding and dyspnea, were more common with ticagrelor administration ($P<0.05$). These findings indicate that ticagrelor offers some outcome advantages over clopidgrel in treating STEMI patients with dementia who undergo PCI, as seen for a broader population, as this intervention can reduce vascular-cause mortality, stroke, and recurrent myocardial infarction risks. Although bleeding was more frequent with ticagrelor treatment, it appeared to be less severe than with clopidogrel treatment.

Keywords: ST elevation myocardial infarction, ticagrelor, percutaneous coronary intervention

Introduction

About 7.25 million people around the world die from coronary heart disease (CHD) each year. In the United States, there are 800,000 newly diagnosed CHD cases each year, while in China, the annual incidence is 120/100,000 [1]. CHD can result in serious adverse events, such as ST-segment elevation myocardial infarction (STEMI), a major type of heart attack. With the aging of the world's population, the incidence of ST-segment elevation myocardial infarction (STEMI) among senile persons is increasing, and half of annual CHD deaths are in senile individuals [2].

Senility, or dementia, describes the progressive loss of 2 or more brain functions, such as memory or language, which occurs more commonly among older individuals [3]. Dementia comprises a constellation of symptoms of diverse etiology, with underlying pathologies including Alzheimer's disease, Parkinson disease, and Lewy body disease [3]. Individuals with dementia face higher surgical risk, thus surgery is not the first-line treatment for co-

morbidities like CHD. However, internal medicine and interventional therapies are widely accepted as tolerated treatment options in this population [4].

In senile individuals, emergency percutaneous coronary intervention (PCI), or the non-surgical insertion of a stent to permit blood flow, is a common treatment following STEMI [5]. Because the central pathological steps of coronary occlusion include platelet activation, adhesion, aggregation, and thrombosis [6], timely and effective antiplatelet therapy after PCI can maintain coronary blood flow and prevent clinical events such as recurrent myocardial infarction and acute coronary stent thrombosis [7]. A new antiplatelet drug, ticagrelor, is a reversible $P2Y_{12}$ receptor blocker that exhibits a stronger, faster, more stable inhibition on the $P2Y_{12}$ receptor, which binds the platelet adenosine diphosphate [7-10]. Ticagrelor requires no activation, has fewer main adverse cardiovascular events, and is gradually being accepted by clinicians. Indeed, the drug can effectively reduce mortality from various cardiovascular events [6, 8-10]. Further, compared to the irreversible $P2Y_{12}$ receptor blocker clopidogrel, ticagrelor can reduce both incidence and mortality of myocardial infarction and cerebral apoplexy in patients with acute coronary syndrome [11]. Despite the advantages of ticagrelor in patients undergoing PCI, little is known about its efficacy in the subset of individuals who exhibit dementia and its associated underlying pathologies.

To determine the utility of ticagrelor as an antiplatelet treatment in individuals with dementia, its efficacy and safety for use after emergency percutaneous coronary intervention were assessed in senile patents with STEMI. A randomized trial was used to compare outcomes of ticagrelor treatment of those with clopidogrel treatment. The findings may help guide treatment practices in for CHD patients with dementia.

Participants and methods

Participants

The study prospectively enrolled 174 patients with both dementia and ST-segment elevation myocardial infarction who were hospitalized in the Cardiology Department of the Fourth Affiliated Hospital, Harbin Medical University from July 2014 to June 2015. Participants agreed to undergo emergency PCI. Criteria for inclusion in the study were: age ≥60 years; acute myocardial infarction within 12 hours after onset of chest pain; and ECG indications of sustained elevation of 2 adjacent ST segments or newly emerging left bundle branch block. Patients were excluded if meeting any of the following criteria: age ≥80 years; presence of chronic obstructive pulmonary disease at acute exacerbation stage, bronchial asthma, malignant tumor, or kidney failure; any contraindication of using clopidogrel, nearly onset cerebral infarction in the last year or previous history of cerebral hemorrhage; severe sinus bradycardia (heart rate <50 beats/min), cardiogenic shock, type II atrioventricular block above degree II, receiving intravenous thrombolysis within 24 h, and currently receiving anticoagulant therapy. This study was approved by the hospital ethics committee, and informed consent was obtained from all participants.

Methods

Grouping: Patients were randomized into two equal groups: one group received clopidogrel treatment and the other group received ticagrelor treatment. The clopidogrel group received a loading dose of 600 mg and then switched to an oral maintenance dose of 75 mg daily. The ticagrelor group received a loading dose of 180 mg and then switched to an oral maintenance dose of 90 mg twice per day. If patients were not already taking aspirin, they received aspirin at a loading dose of 300 mg. After the loading dose of aspiring, patients immediately underwent coronary arteriography and PCI. All patients were closely followed for one month.

There was no statistically significant difference between the two groups of patients for any of the following factors: age, gender, body mass index (BMI) at admission, heart rate at admission, cardiovascular risk factors, previous myocardial infarction, acute anterior myocardial infarction, acute inferior wall myocardial infarction, positive troponin I at entering the study, > class 2 Killip, or myocardial infarction thrombolysis trial (TIMI) risk score ≥3 (P>0.05 for all), as shown in **Table 1** and **Figure 1**.

Observational index

The study groups were observed for 30 days for the main primary outcomes (recurrent myocardial infarction, stroke, or death due to vascular causes) and recurrent severe myocardial isch-

Table 1. Baseline data were compared between two groups of STEMI patients admitted to hospital [n (%)]

Variables	Ticagrelor (n=87)	Clopidogrel (n=87)	χ^2	*P*
Gender			0.093	0.760
Male	48 (55.17)	50 (57.47)		
Female	39 (44.83)	37 (42.53)		
Cardiovascular risk factors				
Smoking	42 (48.28)	39 (44.83)	0.208	0.648
No smoking	45 (51.72)	48 (55.17)		
Hypertension	23 (26.44)	21 (24.14)	0.122	0.727
No hypertension	64 (73.56)	66 (75.86)		
Diabetes	20 (22.99)	15 (17.24)	0.894	0.344
No Diabetes	67 (77.01)	72 (82.76)		
Old myocardial infarction	5 (5.75)	7 (8.05)	0.358	0.550
NO Old myocardial infarction	82 (94.25)	80 (91.95)		
Anterior wall acute myocardial infarction	39 (44.83)	35 (40.23)	0.376	0.540
No anterior wall acute myocardial infarction	48 (55.17)	52 (59.77)		
Acute inferior wall myocardial infarction	23 (26.44)	33 (37.93)	2.633	0.105
No Acute inferior wall myocardial infarction	64 (73.56)	54 (62.07)		
Troponin I-positive at study entry	34 (39.08)	30 (34.48)	0.396	0.529
Troponin I- negative at study entry	53 (60.92)	57 (65.52)		
STEMI risk factors				
Killip>2	5 (5.75)	7 (8.05)	0.358	0.550
Killip≤2	82 (94.25)	80 (91.95)		
TIMI≥3	26 (29.89)	21 (24.14)	0.729	0.393
TIMI<3	61 (70.11)	66 (75.86)		

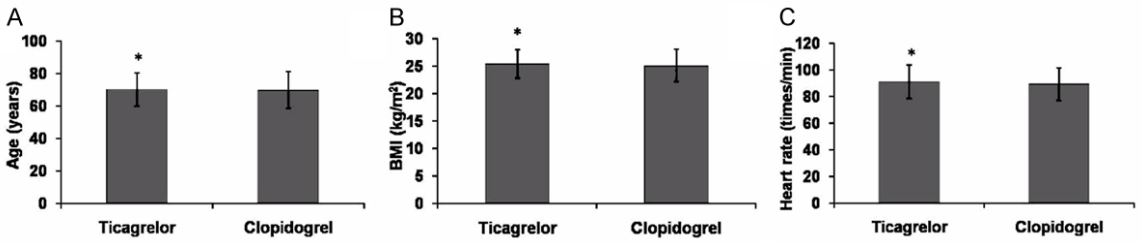

Figure 1. The comparison of age, BMI and heart rate at admission between Ticagrelor and Clopidogrel group. *P>0.05.

emia; coronary stent thrombosis and bleeding events 30 days after surgery, adverse events, including: dyspnea, sinus bradycardia, malignant ventricular arrhythmias, high degree of atrioventricular block, necessity to implant permanent cardiac pacemaker.

Statistical analysis

Data were logged using Epidata 3.1 with a double entry method for accuracy. SAS 9.2 was used for statistical analysis by *t* test, x^2 test, or non-conditional logistic regression. P<0.05 was considered as statistically significant.

Results

Short-term ticagrelor and clopidogrel treatment outcomes during hospitalization

Characteristics of patient treatments, e.g., need for other drug or surgical interventions, were compared during the hospitalization period to determine the short-term outcomes (**Table 2**).

Table 2. Antiplatelet treatment outcomes during hospitalization [n (%)]

Variables	Ticagrelor (n=87)	Clopidogrel (n=87)	χ^2/t	*P*
Antithrombotic therapy during hospitalization				
Aspirin	84 (96.55)	85 (97.70)		0.999*
Unfractionated heparin	63 (72.41)	68 (78.16)	0.772	0.380
Low molecular weight heparin	25 (28.74)	28 (32.18)	0.244	0.621
Bivalirudin	24 (27.59)	18 (20.69)	0.130	0.288
Glycoprotein IIb/IIIa inhibitors	9 (10.34)	10 (11.49)	0.059	0.808
Other drugs used during hospital stay				
β-blockers	50 (57.47)	53 (60.92)	0.214	0.644
Angiotensin converting enzyme inhibitors inhibitors	61 (70.11)	59 (67.82)	0.107	0.743
Atorvastatin calcium	84 (96.55)	83 (95.40)		0.999
Proton pump inhibitors	33 (37.93)	30 (34.48)	0.224	0.636
Implementation of invasive surgery during the study				
Thrombus Aspiration	41 (47.13)	45 (51.72)	0.368	0.544
Onlypercutaneous transluminal coronary angioplasty	14 (16.09)	13 (14.94)	0.044	0.834
Only bare-metal stents	26 (29.89)	23 (26.44)	0.256	0.613
≥1 drug-eluting stents	28 (32.18)	26 (29.89)	0.107	0.743
Vessel TIMI flow 3 class	78 (89.66)	75 (86.21)	0.487	0.485
Failed to open occluded vessels	3 (3.45)	3 (3.45)		1.000
IABP placement	20 (22.99)	22 (25.29)	0.126	0.723
Time from the first dose of antiplatelet drug to Emergency percutaneous coronary intervention	45.91±13.11	47.11±12.9	0.358	0.784

Note: *Fisher's exact test.

Table 3. Endpoint events were compared between two groups within a month [n (%)]

Variable	Ticagrelor (n=87)	Clopidogrel (n=87)	*OR* (95% *CI*)	*P*
The primary endpoint	3 (3.45)	5 (5.75)	0.76 (0.43~0.92)	0.025
Secondary endpoints				
Vascular causes of death	2 (2.30)	4 (4.60)	0.63 (0.34~0.89)	0.020
Recurrent myocardial infarction	1 (1.15)	5 (5.75)	0.55 (0.12~0.79)	0.016
Stroke	2 (2.30)	2 (2.30)		1.000
Recurrent severe myocardial ischemia	4 (4.60)	5 (5.75)	0.61 (0.40~1.14)	0.059
Stent thrombosis	0 (0.00)	4 (4.60)		<0.001

Table 4. Adverse events after one-month drug intervention [n (%)]

Variables	Ticagrelor (n=87)	Clopidogrel (n=87)	*OR* (95% *CI*)	*P*
Upper gastrointestinal bleeding	4 (4.60)	2 (2.30)	2.41 (1.17~3.20)	0.019
Difficulty breathing	12 (13.79)	5 (5.75)	2.04 (1.08~2.98)	0.028
Sinus bradycardia	7 (8.05)	4 (4.60)	1.18 (0.89~1.35)	0.230
Degree atrioventricular block	8 (9.20)	5 (5.75)	1.39 (0.84~1.69)	0.069
Required permanent pacemaker implantation	2 (2.30)	2 (2.30)		1.000
Malignant ventricular arrhythmias	5 (5.75)	6 (6.90)	0.98 (0.81~1.33)	0.510

No statistically significant differences were detected between the treatment groups in the use of anti-thrombosis drugs (aspirin, heparin, bivalirudin, low molecular weight heparin, glycoprotein IIb/IIIa inhibitors) and other drugs (ACEI inhibitors, β-blockers, atorvastatin calcium, proton pump inhibitors) ($P>0.05$ for all). Similarly, no statistical differences were observed in the need for surgical intervention, duration from the first dose of the study drug to PCI, thrombosis suction, only using bare-metal stents, only receiving percutaneous transluminal coronary angioplasty (PTCA), ≥1 drug-eluting stents, class 3 vascular TIMI flow, failing to open occluded blood vessels, or need for implanting intra-aortic balloon pump (IABP) ($P>0.05$ for all).

One-month treatment outcomes in ticagrelor and clopidogrel groups

To assess the long-term efficacy of antiplatelet treatment, the incidence of main endpoint events (death due to vascular causes, cerebral apoplexy, or MI) was assessed (**Table 3**). These events were significantly less common among patients receiving ticagrelor than among those receiving clopidogrel ($P<0.05$). The incidence of cerebral apoplexy was not different between ticagrelor and clopidogrel groups ($P>0.05$), but stent thrombosis was less likely in the ticagrelor group ($P<0.05$).

One-month drug safety in ticagrelor and clopidogrel groups

Adverse events, including drug side effects, were assessed in the one-month follow-up period (**Table 4**). The incidence of upper gastrointestinal hemorrhage was higher in those receiving ticagrelor ($P<0.05$). However, all upper gastrointestinal hemorrhages in the ticagrelor group were non-lethal, while one patient in the clopidogrel group died as a result of this complication. Neither group experienced cerebral hemorrhage. Dyspnea was also significantly more common in the ticagrelor group ($P<0.05$). No statistical differences were detected for the incidence of high-grade atrioventricular block, sinus bradycardia, need for implanting a permanent cardiac pacemaker, or malignant ventricular arrhythmia ($P>0.05$).

Discussion

The application of antiplatelet drugs is standard treatment for patients undergoing PCI. Although clopidogrel is a commonly-used antiplatelet drug, its effects require biotransformation with cytochrome P450 isozymes to induce irreversible binding with the $P2Y_{12}$ receptor. In contrast, the reversible binding of ticagrelor occurs rapidly after oral ingestion, with an average half-life of approximately 7 h, and its reversible action helps reduce the risk of bleeding [8-11]. This drug offers several advantages over clopidogrel, but its safety and effi-

cacy in senile patients with STEMI, who have other diseases underlying their dementia, was previously unknown. In contrast, clopidogrel has been studied in this population. One study found that failure to fill a clopidogrel prescription is associated with a higher risk of death in the 3 months following stent implantation among older individuals with dementia [12]. Thus, there is clinical value in understanding the safety and efficacy of antiplatelet treatments in this population.

In this study, the incidence of main endpoint events (death due to vascular causes, cerebral apoplexy, or MI) and stent thrombosis was lower in patients receiving ticagrelor than that in patients receiving clopidogrel. Thus, the efficacy of ticagrelor appears to offer an improvement over clopidogrel in this patient subset. In contrast, adverse events like upper gastrointestinal hemorrhage and dyspnea were more common in the ticagrelor group; therefore treatment plans should consider the potential side effects of ticagrelor treatment.

The findings in this study were consistent with those of Wallentin et al. [11]. Interestingly, Brott et al. [13] found that platelet aggregation reactivity of patients with acute coronary stent thrombosis is high, which was attributable to clopidogrel resistance. Ticagrelor offers the potential to bypass the shortcomings of clopidogrel by providing a faster platelet aggregation inhibition [13, 14]. Thus, the ability of ticagrelor to improve survival rates after emergency PCI in senile STEMI patients may be correlated with decreased risk of stent thrombosis events.

For senile patients who are usually complicated by diseases from other systems, therapeutic safety should be taken into consideration. Ticagrelor can increase atrioventricular disorder, which is correlated with its ability to inhibit erythrocyte's uptake of adenosine [15, 16]; therefore, in case of high-grade atrioventricular block, ticagrelor should be discontinued as soon as possible, switching to clopidogrel, to further shorten indwelling time of temporary cardiac pacemaker, reduce deep venous thrombosis of lower limbs, pulmonary embolism, and other events. The current study found that, compared to clopidogrel, ticagrelor is more likely to promote dyspnea, which may be due to the fact that ticagrelor and ATP have similar chemical structure, which will produce cytarabine-like bronchial irritation [17, 18]. Therefore, those unable to tolerate dyspnea should discontinue ticagrelor. Despite these drawbacks, the application of ticagrelor in acute coronary syndrome can reduce main adverse cardiovascular events, without increasing severe bleeding, which is similar to other findings [10, 19-21]. Larger patient populations should be assessed to confirm the safety and efficacy of ticagrelor in individuals with dementia, but these preliminary findings provide a foundation upon which to explore treatment paradigms including ticagrelor among this patient subset.

Disclosure of conflict of interest

None.

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