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Effects of Thrombus Aspiration Catheter Combined with Atorvastatin in Reducing No-Reflow Phenomenon in Emergency Percutaneous Coronary Intervention for Acute Myocardial Infarction

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ABSTRACT

Objective: To explore therapeutic effects of thrombus aspiration catheter (TAC) combined with atorvastatin in reducing no-reflow in emergency percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

Methods: A total of 126 AMI patients from January 2012 to June 2014 undergoing PCI but with slow flow or no-reflow were chosen as the study participants and divided into atorvastatin group and control group, each with 63 cases. The atorvastatin group received TAC treatment combined with atorvastatin while the control group received standard PCI treatment. Clinical records were then collected and analysed, including plasma high sensitive c-reactive protein (Hs-CRP) and soluble cell adhesion molecule-1 (sICAM-1) and serum pro B type natriuretic peptide (Pro-BNP). Thrombolysis in myocardial infarction (TIMI) grade 3 flow, heart function parameters and conditions of prognosis were also detected.

Results: Preoperative and 24 h postoperative plasma Hs-CRP and sICAM-1 levels, and postoperative serum Pro-BNP level were lower in the atorvastatin group than those in the control group (all $P<0.05$). The percentages of infarct related artery (IRA) with TIMI grade 3 flow and postoperative ST segment resolution > 50% were higher, while creatine kinase-MB isoenzyme (CKMB) peak value, CKMB peak time, and occurrence rates of IRA no-reflow/slow flow and major adverse cardiovascular event (MACE) were lower in the atorvastatin group than those in the control group (all $P<0.05$).

Conclusion: TAC combined with atorvastatin in the treatment of AMI patients after emergency PCI is safe, effective and worthy of clinical application.

INTRODUCTION

Acute myocardial infarction (AMI) is caused by myocardial tissue necrosis due to vascular occlusion of coronary artery acute and persistent ischemia and has typical symptoms include chest pain, chest tightness, arrhythmia, and heart failure [1].

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AMI is a disease common in the emergency department, and according to statistics, 5%~10% of the patients suffering chest pain in emergency departments is caused by AMI [2]. As the most effective means of treating AMI in the emergency department, percutaneous coronary intervention (PCI) can restore cardiac muscle tissue perfusion by reducing the area of myocardial infarction and improving left ventricular ejection fraction [3]. However, for some patients with AMI in PCI treatment, even if the infarction related artery (IRA) was restored, the necrosis of the myocardial tissue was still not effective, and such phenomenon is called no-reflow [4]. No-reflow phenomenon is an important indication for poor prognosis after PCI treatment, so it is one of the important goals of AMI reperfusion therapy to reduce the occurrence of no-reflow phenomenon [5]. At present, the mechanism of the occurrence of no-reflow phenomenon is still not clear, but it is safe to say that this phenomenon is related to such factors as embolization, ischemia reperfusion injury, and microcirculation disturbance [6].

Atorvastatin is a kind of HMG-CoA reductase inhibitor and its main function is to reduce the human body cholesterol and triglyceride contents [7]. Recent studies have proved that atorvastatin is conducive to the regulation of body fat and protection of myocardial tissue [7,8]. Research indicates that statins can reduce the no-reflow phenomenon occurrence rate after AMI reperfusion and taking atorvastatin twelve hours before undergoing operation can enhance the effect of PCI Treatment and improve the prognosis [9]. Besides, thrombus aspiration catheter (TAC) can achieve ideal treatment effect on patients with myocardial infarction after PCI treatment through suction and removal of intracoronary thrombus aspiration [10].

However, few articles elaborate the therapeutic effects of thrombus aspiration catheter (TAC) combined with atorvastatin in reducing no-reflow phenomenon in emergency PCI for AMI patients. This study takes AMI patients with no-reflow phenomenon after PCI surgery as study subjects. The atorvastatin group was treated with thrombus aspiration combined with atorvastatin compared with the control group with conventional PCI treatment. The plasma Hs-CRP, sICAM-1, serum Pro-BNP levels were then evaluated along with the conventional indicators.

MATERIALS AND METHODS

Participants

A total of 126 AMI patients from January 2012 to June 2014 undergoing PCI but with slow flow or no-reflow at our hospital were chosen as the study participants, including 69 males and 57 females with a mean age of 65.0 ± 7.9. According to the random number table method, patients were randomly assigned to thrombus aspiration combined with atorvastatin treated group (atorvastatin group) and standard PCI group (control group), each with 63 cases. Inclusion criteria: patients were in line with the diagnostic criteria of AMI in the World Health Organization [11]. After restoring IRA, coronary artery angiography results showed that the distal blood flow significantly slowed down (TIMI 2 grade, slow flow) or lost (TIMI 0~1, no-reflow), and no endometrial tears, dissection, thrombus embolism and other mechanical obstruction. Exclusion criteria: patients with severe infection, severe liver or kidney damage, malignant tumor, coagulation dysfunction, etc. The study was approved by the ethics committee of the author's working hospital, and all the subjects signed the informed consent. All procedures in this study were in compliance with the Declaration of Helsinki [12].

Therapy

Two groups of patients were treated with emergency PCI operation within 12 hours since the onset of the illness. Six hundred mg clopidogrel and 300 mg aspirin were given before operation, and 3000 units of heparin was injected to the patients with 100 U/kg added during the operation and an additional 1000 units added per extended operation hour. Coronary angiography and PCI were performed by the standard Seldinger method through the radial artery or femoral artery way. The planted stent diameter was selected according to (1-1.1)/1 ratio. The drug eluting stent completely covered the lesion with a release pressure of 808 to 1944 kPa. The patients in the control group were treated with conventional medicine therapy of aspirin, clopidogrel, low molecular weight heparin and atorvastatin, tirofiban before and after the PCI operation, and angiotensin-converting enzyme inhibitor (ACEI) agents and beta blockers according to blood pressure and heart rate. Patients in the atorvastatin group were treated with 80 mg of atorvastatin intensive treatment, and the GOODMAN thrombus aspiration device was used in the treatment consisting of a 136 cm-long 6F double-channel catheter with an inner diameter of 1.1 mm and a 30 ml-syringe at one end. First, a 0.36 mm of the guide wire was sent to the distal end of the IRA, and then double-channel catheter was guided down to IRA along the wire. The catheter was placed under X-ray and right in the section of the thrombus formation, and connected with the syringe to conduct suction, at the same time the catheter was gently moved back and forth to avoid air getting into the coronary artery from the catheter. After the PCI operation, all patients were given 0.075-0.150 μg/kg·min) of GPIIb/IIIa, a kind of receptor antagonist, instead of tirofiban, in 36 consecutive hours. Conventional medications such as statins and beta blockers were administered and the basic diseases (hypertension, hyperlipidemia and diabetes) also received well treated. The clinical baseline data were collected, including age, sex, blood lipids, smoking status, and time of onset. The left ventricular ejection fraction (LVEF) and left ventricular end diastolic (LVED) of patients in two groups were measured.

Measurement of Serum Hs-CRP and sICAM-1

Venous blood samples (10 ml) of all patients were collected before operation and 24 hours after operation , of which 6 ml was injected into two $EDTANa_2$ anticoagulant tubes stored at -80°C, each with 3 ml. The remaining blood samples were used to

test Pro-BNP. Coulter Image (Beckman, USA), an immune biochemical detector, was used to determine the plasma HsCRP by the turbidity measurement. Enzyme-linked immunoassay (ELISA) Kit (R&D system, UK) was used to determine plasma sICAM-1.

Measurement of Serum Pro-BNP

Participants were fasted overnight at 7 days, 1 month, 3 months after operation, and in the early morning, venous blood (3 ml) was collected in the vacuum blood collection tube, and immediately centrifuged for 10 minutes (3000 r/min). Serum samples were collected separately and stored at -20°C. The concentration of Pro-BNP was determined within two weeks by Roche pro-BNP kit and with electrochemical luminescence immunoassay on Roche Elecsys. The results showed coefficients of variation (CVs) of 2.2%-5.8%.

Postoperative Indicator Observation

The following postoperative indicators were observed: (1) Slow flow or no-reflow refers to the phenomenon that although the coronary stenosis was relieved, the distal blood flow was significantly reduced (TIMI grade 2, slow blood flow) or lost (TIMI grade 0 to 1, no-reflow). Blood flow of the infarct vessel was recorded. (2) One hour after the operation, the electrocardiogram was rechecked. The highest ST segment resolution was observed. And the ST segment resolution percentage was calculated as: the difference of the ST segment elevation before and after the operation dividing the preoperative ST segment elevation value. (3) Myocardial enzyme marker detection: peak value of creatine kinase-MB isoenzyme (CKMB) after operation was detected. (4) Echocardiography was performed 1 week and 3 months after surgery, and left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVDD) were recorded. (5) Major adverse cardiac events (MACEs) were recorded 30 days after the operation including death, myocardial infarction, target vessel revascularization and stroke. (6) Postoperative bleeding: according to the TIMI grading standard, massive hemorrhage (intracranial hemorrhage or hemorrhage of digestive tract) were recorded.

Statistical Analysis

Data were statistically analyzed by SPSS 20 (SPSS Inc., Chicago, IL, USA). The measurement data were expressed by mean ± standard deviation (SD) and were compared by t test. Enumeration data were presented as percentage or rate and were compared with the chi square test. Two-sided *P* value of less than 0.05 was considered statistically significant.

RESULTS

General Information Comparisons

The levels of total cholesterol (TC) and total glyceride (TG) were significantly lower in atorvastatin group than those in control group (both $P<0.05$). However, there were no significant statistical differences in age, gender, smoking status, diabetes, hypertension, stroke, low density lipoprotein, time of onset, renal function, TIMI, IRA, IRA, etc. between the two groups as were shown in **Table 1.**

Table 1. General information comparison between atorvastatin group and control group.

General information	Atorvastatin group (n=63)	Control group (n=63)	t/F	P
Age (years)	65.0 ± 7.9	64.5 ± 6.7	0.383	0.702
Gender (male/female)	34/29	35/22	0.677	0.411
Smoking condition (%)	30 (47.6%)	21 (33.3%)	2.668	0.102
Diabetes (%)	29 (46.0%)	24 (38.1%)	0.680	0.410
Hypertension (%)	50 (79.4%)	42 (66.7%)	2.578	0.108
Stroke (%)	10 (15.9%)	7 (11.1%)	0.612	0.434
TC(mmol/l)	4.99 ± 0.44	5.20 ± 0.54	2.393	0.018
TG(mmol/l)	2.61 ± 1.03	3.02 ± 1.08	2.181	0.031
Low density lipoprotein	3.12 ± 0.93	2.95 ± 0.86	1.065	0.289
(mmol/l)				
Illness duration (h)	7.60 ± 2.01	8.20 ± 2.51	1.488	0.140
renal inadequacy	8 (12.7%)	4 (6.3%)	1.474	0.225
TIMI blood flow				
Grade 1	42 (66.7%)	34 (54.0%)	3.742	0.154
Grade 2	15 (23.8%)	25 (39.7%)		
Grade 3	6 (9.5%)	4 (6.3%)		
IRA distribution				
LAD	31 (49.2%)	29 (46.0%)	0.344	0.842
LCX	15 (23.8%)	14 (22.2%)		
RCA	17 (27.0%)	20 (31.8%)		

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Note: TC: cholesterol total; TG: triglyceride; TIMI: thrombolysis in myocardial infarction; IRA: infarct related artery; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery

Comparisons of Plasma Hs-CRP and sICAM-1 in the Atorvastatin Group and the Control Group

The plasma Hs-CRP levels were (5.26 ± 1.62) (mg/L) and (7.41 ± 2.53) (mg/L) before operation and 24 hours after operation in the atorvastatin group and were (6.02 ± 1.75) (mg/L) and (8.45 ± 2.61) (mg/L) in the control group. Preoperative and 24 h postoperative plasma Hs-CRP levels in the atorvastatin group were lower than the control group with statistically significant difference (both $P<0.05$). And there were significant differences in the Hs-CRP levels in the same group before and after operation (both $P<0.05$). Preoperative and 24 h postoperative plasma sICAM-1 in the atorvastatin group were (215.36 ± 33.45) (μg/L) and (232.25 ± 42.01) (μg/L), and (296.45 ± 46.25) (μg/L) and (319.36 ± 71.12) (μg/L) in the control group. Significantly lower preoperative and postoperative plasma sICAM-1 was in found in the atorvastatin group than those in control group (both $P<0.05$). And there were significant differences in the sICAM-1 level in the same group before and after operation (both $P<0.05$) **(Table 2 and Figure 1).**

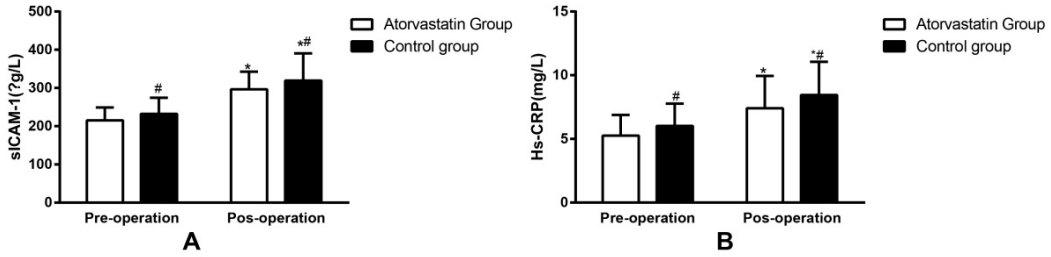

Figure 1. Comparison of levels of Hs-CRP and sICAM-1.

Note:*, Comparison within the same group before the operation, $P<0.05$ #; Comparison between the atorvastatin group and the control group at the same time point, $P<0.05$.

Hs-CRP: high sensitive C - reactive protein; sICAM-1: soluble cell adhesion molecule-1.

Table 2. Comparison of levels of Hs-CRP and sICAM-1 in atorvastatin group and control group.

Indicators	Testing time	Atorvastatin group (n=63)	Control group (n=63)	t	P
Hs-CRP(mg/L)	Pre-operation	5.26 ± 1.62	6.02 ± 1.75	2.530	0.013
	Post-operation (24 h)	7.41 ± 2.53*	8.45 ± 2.61*	2.271	0.025
sICAM-1(μg/L)	Pre-operation	215.36 ± 33.45	232.25 ± 42.01	2.496	0.014
	Post-operation (24 h)	296.45 ± 46.25*	319.36 ± 71.12*	2.143	0.034

Note:*, comparison between post-operation (24 h) and pre-operation within the same group, $P<0.05$. Hs-CRP: high sensitive C - reactive protein; sICAM-1: soluble cell adhesion molecule-1.

Pre-operative and Post-operative Pro-BNP Level Comparisons

In the atorvastatin group, the preoperative Pro-BNP levels were significantly higher than the Pro-BNP levels in every time point during the postoperative period (all $P<0.05$). Pro-BNP level decreased gradually with the prolongation of the time after the operation with significant differences among each time point (all $P<0.05$). The change trend of Pro-BNP level in control group was similar to that of the atorvastatin group. Postoperative 1 day, 7 days, 1 month and 3 months, the pro-BNP levels in the control group were higher than those in the atorvastatin group (all $P<0.05$), while there was no significant difference in Pro-BNP level between the two groups before operation **(Table 3 and Figure 2).**

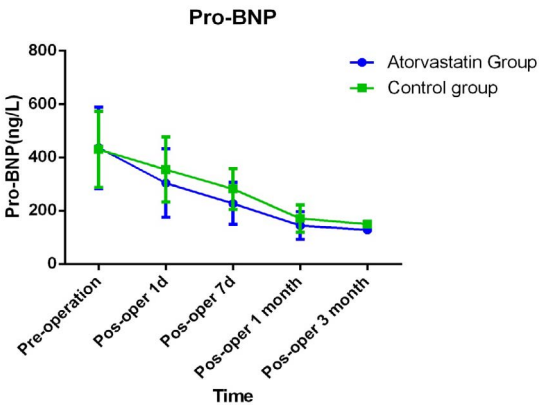

Figure 2. Pre-operative and post-operative Pro-BNP level comparison.

Note:*, Pro-BNP: pro B type natriuretic peptide

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Table 3. Pre-operative and post-operative Pro-BNP level comparisons

Group	Pre-operation	1 d after operation	7 d after operation	1 m after operation	3 m after operation
Atorvastatin	436.0 ± 152.6	303.5 ± 128·6#	226.9 ± 78.9#▲	144.5 ± 52.3#▲•	128.6 ± 9.7#▲•◆
Control	429.6 ± 142.5	354.6 ± 122.5*#	281.6 ± 76.4*#▲	171.0 ± 51.1*#▲	149.6 ± 12.4*#▲•◆

Note: *comparison between two groups at the same time point, *P*<0.05; #: Pre-operative comparison within the same group, *P*<0.05; ▲: One day after operation comparison within the same group, *P*<0.05; •: Seven days after operation comparison within the same group, *P*<0.05; ◆: Three months after operation comparison within the same group, *P*<0.05.

Post-operative TIMI Grade 3 Flow, Heart Function Parameters and Prognosis

The percentages of infarct related artery (IRA) with TIMI grade 3 flow and postoperative ST segment resolution > 50% were higher, while creatine kinase-MB isoenzyme (CKMB) peak value, CKMB peak time, and occurrence rates of IRA slow flow or re-flow and major adverse cardiovascular events (MACEs) were lower in the atorvastatin group than those in the control group (all *P*<0.05) The atorvastatin group 3 months after operations saw a higher level of LVEF, while a lower level of LVDD than that of the control group (*P*<0.05). One week after operation, the differences of LVEF, LVDD and hemorrhage cases in the atorvastatin group and control group were not statistically significant (all *P*<0.05) **(Table 4).**

Table 4. Post-operative TIMI grade 3 blood flow, heart function parameters and prognosis

Indicators	Atorvastatin group (n=63)	Control group (n=63)	t/F	P
IRA grade 3 blood flow	45 (71.4%)	31 (49.2%)	5.885	0.015
Post-operation 2 h ST-	36 (57.1%)	24 (38.1%)	4.582	0.032
segment resolution > 50%				
CKMB peak value (U/L)	179 ± 36	201 ± 58	2.558	0.012
CKMB peak time (h)	12 ± 6	15 ± 7	2.329	0.022
IRA no/low reflow	3 (4.8%)	10 (15.9%)	4.203	0.040
One week after operation				
LVEF (%)	56 ± 9	54 ± 7	1.392	0.167
LVDD (mm)	43 ± 5	44 ± 6	1.016	0.312
Three months after operation				
LVEF (%)	52 ± 9	49 ± 6	2.201	0.029
LVDD (mm)	44 ± 6	47 ± 8	2.381	0.019
MACE occurrence rate	1 (1.6%)	8 (12.7%)	5.863	0.016
Hemorrhage cases	2 (3.2%)	1 (1.6%)	0.342	0.559

Note: IRA: Infarct Related Artery; TIMI3: Thrombolysis in Myocardial Infarction 3; CKMB: MB Isoenzyme of Creatine Kinase; LVEF: Left Ventricle Ejection Fraction; LVDD: Left Ventricular Diastolic Dimension; MACE: Major Adverse Cardiac Events.

DISCUSSION

The no-reflow phenomenon is one of the most serious complications after PCI treatment in AMI patients, and how to reduce the incidence rate and the mortality of patients is an important objective for the treatment of AMI for cardiac physicians [13]. In this study, we applied the method of thrombus aspiration catheter combined with atorvastatin in the treatment AMI patients after emergency PCI therapy. In comparison with the control group, satisfactory results were obtained in the atorvastatin group in terms of efficacy and safety.

In the experiment, the levels of Pro-BNP, sICAM-1 and Hs-CRP in each operation period of the atorvastatin group were lower than those in the control group. Hs-CRP, sICAM-1, and Pro-BNP are the bio-markers of such acute coronary syndrome as AMI and they play an important role in in the early diagnosis of diseases, disease stratification and prognosis assessment and beyond [14]. As a major risk factor for AMI, Hs-CRP is associated with the vulnerability of coronary atherosclerotic plaques, and the increased level of Hs-CRP indicates an increased incidence of cardiovascular disease in the future [15]. In many cases, the mechanical effect of the operation can cause the plaque damage in blood vessels in the PCI treatment, which leads to the formation of micro thrombosis, causing no-reflow [16]. In the present study, the levels of Hs-CRP were decreased, which indicated that the application of this method can reduce the vulnerability of the plaque, so as to reduce the incidence of no-reflow. SICAM-1 is one of the members of the immunoglobulin superfamily, and is involved in the immune response and antigen presentation Dong et al. [17], found that the occurrence and development of AMI were closely related to inflammation, and the levels of inflammatory mediators, including sICAM-1, were elevated in AMI patients [18]. In recent years, studies showed that atorvastatin statins is pleiotropic and have anti-inflammatory effect [19,20]. After treatment, sICAM-1 level decreased indicating that the test method reduced the AMI inflammation. Pro-BNP is an early diagnostic indicator of AMI and AMI patients with myocardial perfusion deficiency will lead to cardiac hemodynamic changes, causing left ventricular filling, lifted left ventricular filling pressure, thereby promoting the synthesis and secretion of Pro-BNP [21]. Hong et al. pointed out those preoperative serum NT Pro-BNP levels of AMI patients can

be used as an important predictor of postoperative no-reflow [22]. In the present study, the use of thrombus aspiration combined with atorvastatin in the treatment enables the myocardial tissue appropriate perfusion along with the recovery of left ventricular function and decrease of Pro-BNP synthesis.

The postoperative conventional indicators showed that the percentages of infarct related artery (IRA) with TIMI grade 3 flow and postoperative ST segment resolution > 50% were higher and that occurrence rates of IRA slow flow or no-reflow were lower in the atorvastatin group than those in the control group. All the above results indicated that thrombus aspiration combined with atorvastatin in PCI treatment reduces the load of thrombosis in coronary artery, thereby reducing the risk of micro emboli falling, responsible for no-reflow after PCI treatment [23]. As a classic indicator of AMI, CKMB has a high specificity and sensitivity to AMI, and is an ideal marker for laboratory diagnosis of AMI [24]. The fact that CKMB peak and CKMB peak time in atorvastatin group were lower than that in the control group reflected the application of thrombus aspiration combined with atorvastatin improved impatient hypo perfusion; further suggesting PCI treatment had achieved the ideal effect [25]. According to the study data, atorvastatin group saw a higher level of LVEF and a lower level of LVDD than those of the control group. Also, occurrence rate of MACEs was lower in the atorvastatin group. All indicated that thrombus aspiration combined with atorvastatin were effective in the treatment of AMI after PCI.

Study has indicated that, in addition to the regulation of body fat, statins can also regulate endothelial function, reduce the number of adhesion molecules, reduce inflammatory markers in circulation and protect the myocardial tissue Zhao et al. [26], pointed out that in a rabbit model, the single dose of atorvastatin has an anti-inflammatory effect, could reduce the occurrence of no-reflow as well as the infarct size in the AMI reperfusion therapy [27]. Also in the rabbit model, Shao et al. confirmed that preoperative use of atorvastatin could improve hemodynamics, reduces the body inflammatory markers as well as incidence of no-reflow [28]. Zhou et al. found that combination of thrombus aspiration, high dose preoperative statins, and adenosine in the operation can reduce the occurrence of no-reflow phenomenon after the PCI treatment [29]. The use of atorvastatin, on the one hand, stabilizes the IRA internal carotid plaque status, reduces the formation of micro embolism caused by plaque rupture; On the other hand, the anti-inflammatory effect of atorvastatin reduces the inflammatory mediators in the blood, and alleviates the inflammatory response of AMI; and at the same time, the use of thrombus aspiration can also be more effective in distal thrombus removal, dredging vessels, reducing the load of coronary artery, improving hemodynamics, thus achieving better therapeutic effect [30].

In this study, the thrombus aspiration catheter combined with atorvastatin was applied to the treatment of no-reflow phenomenon for emergency PCI. By observing the conventional indicators and special biological markers, we found that thrombus aspiration combined with atorvastatin in the treatment of AMI were safe, effective and worthy of clinical application.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

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