Received: 9 January 2019 | Accepted: 20 January 2019

DOI: 10.1002/ccd.28112

WILEY

ORIGINAL STUDIES

Comparison of myocardial microcirculatory perfusion after catheter-administered intracoronary thrombolysis with anisodamine versus standard thrombus aspiration in patients with ST-elevation myocardial infarction

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Abstract

Objective: To evaluate efficacy, safety and feasibility of targeted intracoronary injection using pro-urokinase combined with anisodamine (TCA) versus thrombus aspiration (TA) in ST-elevation myocardial infarction (STEMI) patients with high thrombus loads.

Background: The best method of avoiding thrombus detachment and stroke in PCI patients with high thrombus loads has not yet been established.

Methods: STEMI patients receiving coronary artery angiography or percutaneous coronary intervention (CAG/PCI) with thrombus grade ≥ 3 from January 1, 2017 to June 30, 2018 were randomly assigned to targeted intracoronary thrombolysis (pro-urokinase and anisodamine via catheter (TCA) group), or the TA group which followed the standard thrombus aspiration procedure. Parameters compared included thrombus grade, index of microcirculatory resistance (IMR), postoperative myocardial SPECT, thrombosis in myocardial infarction (TIMI) scores including flow grade, corrected TIMI frame counts (CTFCs), and TIMI myocardial perfusion grade (TMPG). Adverse events were followed up within 3 months.

Results: Thirty-nine patients were finally enrolled. In primary CAG/PCI, the TCA group had higher percentages of TIMI 3 flow and lower IMR values compared with the TA group. The ratio of TMPG 3 grade in the TCA group was higher in repeat CAG, and the perfusion descending area (PDA) presented by SPECT was lower than in the TA group. No significant difference was seen in major adverse coronary events (MACEs) or bleeding events at follow-up.

Conclusions: TCA appears to be effective, safe, and feasible for repatency and reduction of high thrombus burden in primary PCI and may protect myocardial microcirculation with improved outcomes.

KEYWORDS

anisodamine, percutaneous aspiration thrombectomy, percutaneous coronary intervention, pro-urokinase, ST-elevation myocardial infarction, thrombolytic therapy

1 | INTRODUCTION

In primary PCI treatment for ST-elevation myocardial infarction (STEMI), severe thrombus load is very common in many infarct-related arteries (IRAs).[1] A high thrombus load (grade 3 or higher) not only directly occludes the IRA, but also generates thrombotic micro-debris to further obstruct the myocardial microcirculatory system. A quick, effective, and safe clearance of thrombosis in the IRA plays a key role

in reperfusion treatment in STEMI patients with high thrombus loads. Otherwise, it risk worsening the stenosis or causing re-occlusion in IRAs, and potentially extending the area of myocardial infarction and dysfunctional myocardial microcirculation, in turn resulting in severe complications such as acute heart failure, cardiac shock, and sudden death.

Vacuum aspiration via catheter is one effective approach to high thrombus loads, and is widely used in present PCI technique. However, recent prospective randomized clinical trials (such as the TASTE and TOTAL studies) have indicated that patients receiving thrombus aspiration techniques gained no benefit compared with those receiving regular PCI.[2,3] What is more, thrombus aspiration appears to increase the risk of thrombus detachment and stroke.

The technique of targeted intracoronary thrombolysis is another approach for treatment of high coronary thrombus load. This approach is based on the mechanism of chemical disintegration and melting of thrombi, rather than suction or other mechanical manipulation of thrombi. Therefore, it averts distal obstruction of the myocardial microvascular system with consequent degradation of myocardial reperfusion. Promisingly, the new generation of thrombolytics such as pro-urokinase have a characteristic of high selectivity and rapid fibrolysis of coronary thrombi.[4,5] Targeted intracoronary thrombolysis with these new-generation thrombolytics shows improved efficacy and safety in clearance of coronary thrombosis in several studies.

Anisodamine is a medicine with multiple pharmacologic mechanisms which can effectively improve microcirculatory perfusion in shock and frostbite and diminish ischemic reperfusion injury.[6] Our previous preclinical and clinical research on this medicine over 20 years indicates anisodamine is effective for clearing STEMI patients' myocardial microcirculation.[7–9] Especially for those with severe myocardial infarction, it can also increase mean coronary perfusion pressure, enhance tolerance for ischemia and anoxia, and maintain the stability of myocardial electrophysiology. These characteristics hold obvious potential benefit in the treatment of STEMI patients with high thrombus loads.

For these reasons, we designed this prospective randomized controlled trial to compare efficacy and safety between the strategy of targeted intracoronary thrombolysis with pro-urokinase combined with anisodamine via intracoronary injection, and the strategy of classic intracoronary thrombus aspiration, in order to explore a safer and more feasible and effective treatment in STEMI patients with high thrombus loads.

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 130 consecutive patients with first STEMI receiving primary PCI within 12 hr were admitted to Second Hospital of Hebei Medical University and its cooperative hospitals from January 1, 2017 to June 30, 2018. All patients were confirmed with clinical evidence of STEMI by the 2017 European Society of Cardiology diagnosis standards,[10] which includes: (a) chest pain for more than 30 min unrelieved by use of nitrates; and (b) ECG showing dynamic changes on at least two adjacent leads, elevated by no less than 0.2 mV (precordial leads), or 0.1 mV (limb leads), or a new-onset left bundle branch block.

Exclusion criteria included: thrombus load less than grade 3 in angiography; prior intravenous thrombolysis treatment; cardiac shock; unsuitability of opening IRA; severe infection; hepatic injury; renal dysfunction requiring dialysis; allergy to heparin, aspirin, contrast, thrombolytic or anisodamine; refusal to participate; and other conditions considered to render the patient not appropriate for this trial.

After exclusion by the criteria, the enrolled patients were 1:1 randomized into the thrombolysis combined with anisodamine group (TCA group) or the thrombus aspiration group (TA group). During the following PCI, in the TA group, when we failed to appropriately place thrombus aspiration catheter to perform a successful aspiration, the patient would be transferred to TCA group and received intracoronary thrombolysis and anisodamine treatment. The patients of TCA group who was not able to receive a successful thrombolysis procedure for such as the thrombolysis catheter could not approach to the target thrombus or anisodamine injecting failure would be eliminated due to the thrombolytic already injected might disturb the result of the trial.

Patients were selected, randomized, and followed up according to the flowchart given in Figure 1.

All included subjects gave written, informed consent to the study, which was approved by the ethics committee of Second Hospital of Hebei Medical University.

2.2 | Study protocol

2.2.1 | Coronary angiography and PCI

Routine coronary angiography (CAG) was performed via radial artery. After identifying the IRA, the grade of stenosis, grade of thrombus load, thrombosis in myocardial infarction (TIMI) flow grade, corrected TIMI frame count (CTFC), and TIMI myocardial perfusion grade (TMPG) were measured.

2.2.2 | TCA group

Targeted intracoronary thrombolysis was performed by appropriate catheter technique, utilizing Finecross microcatheter (NC-F863A, TERUMO, Tokyo, Japan), child-in-mother catheter and/or pierced balloon according to indications, to inject slowly and uniformly pro-urokinase (5 mg:10 mL: Tasly Group, Tianjin, China) as close as possible to the coronary thrombosis. The total injection time was between 5 and 10 min, and the injection dose was 10–20 mg according to the practical situation. After 15–30 min, angiography was performed again to evaluate the results, including all the values previously measured. Then stents were implanted if indicated.

Two anisodamine injections were also sequentially performed using the above technique. The first injection was carried out at the time the thrombolytic was injected, and the second was at the end of the thrombolysis period, just before the final angiography. Each injection dose of anisodamine is 4 mg (4 mg:10 mL, Tianjin Pharmaceuticals, Tianjin, China).

2.2.3 | TA group

Routine coronary aspiration was performed in the TA group patients. Using the Export AP aspiration catheter (Medtronic Cardiovascular,

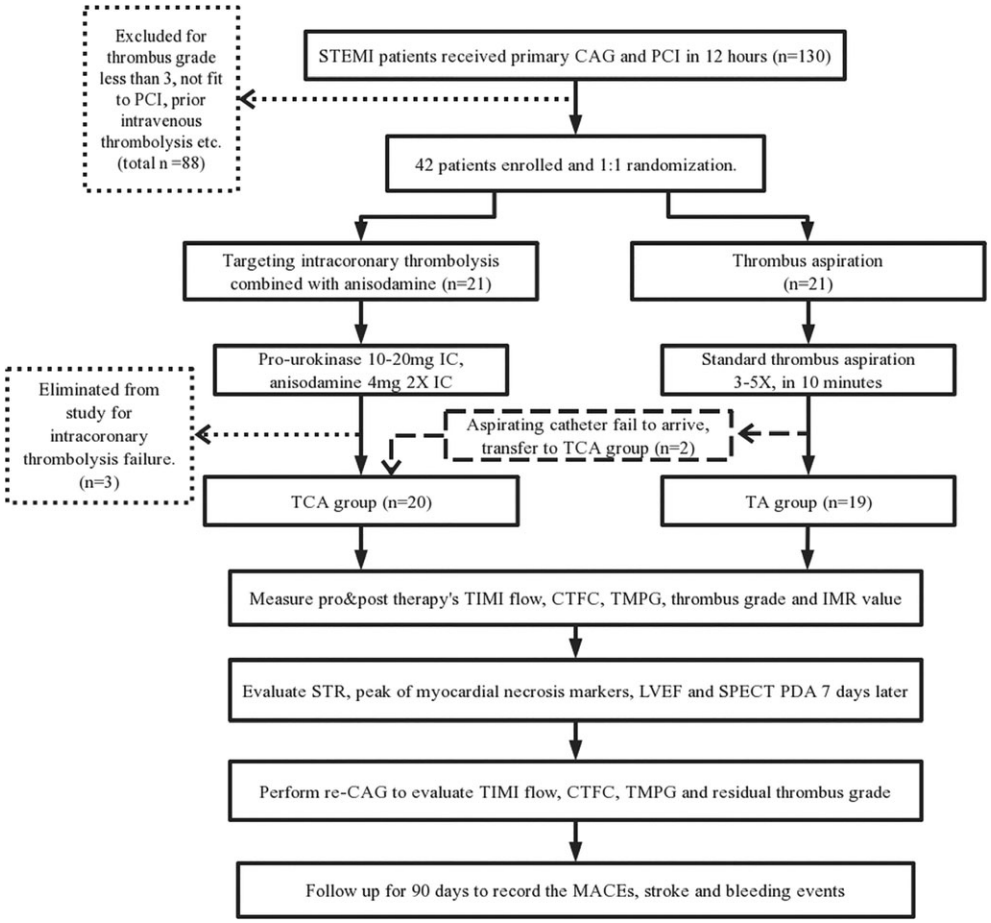

FIGURE 1 Flowchart of the study design

CA), 3–5 applications of vacuum suction with 60 mL volume per suction were performed over no more than 10 min. After that, we performed a second angiography to evaluate the result, and implanted stents if indicated.

2.2.4 | IMR examination

We used the arterial physiologic detector (RadiAnalyzer Xpress 12,711, St. Jude Medical System, Uppsala, Sweden) to perform an index of microcirculatory resistance (IMR) measurement by placing a special PressureWire (C12008, St. Jude Medical System AB, Uppsala, Sweden) at the distal segment of the IRA under maximal hyperemia induced with a standard dose of adenosine triphosphate, thus measuring the IMR value immediately by bolus injecting saline.

2.2.5 | Echocardiography, SPECT, ECG, and re-CAG examination after 7 days

Seven days after the first CAG and PCI, all patients received echocardiography examinations to measure the left ventricular ejection fraction (LVEF). Standard ^{99}Tc-MIBI SPECT myocardial perfusion imaging was taken and the perfusion defect area (PDA) was analyzed by two blinded nuclear radiologists. ST-segment restoration was measured by ECG exam; a decrease in the sum of ST-segment elevation by ≥50% was categorized as complete ST-segment resolution (STR). A CAG exam was performed again no less than 7 days later to evaluate the results of the first angiography and PCI treatment. TIMI flow grade, CTFC, and TMPG were assessed again during this angiography to compare with the prior values. The primary endpoint was TMPG 3 in the repeat CAG.

2.2.6 | 90-Day follow-up

All patients received routine medical therapy include dual antiplatelet treatment (Aspirin with Ticagrelor or Clopidogrel), β-blocker, and ACEI/ARB. By outpatient and telephone follow up, major adverse coronary events (MACEs) (cardiac death, reinfarction, and malignant arrhythmia, etc.) and bleeding complications were recorded. MACE occurrence at 90-day follow-up was defined as the secondary endpoint.

2.2.7 | Statistics method

All analyses were performed with the SPSS 20.0 software (IBM, Armonk, NY). Continuous variables were examined by Levene's method, then expressed as mean ± standard deviation (SD) and median (Q25%, Q75%), and categorical variables were reported as frequency n (%). Student's t or Fisher's test or Mann–Whitney U test was used when appropriate. $p < 0.05$ was considered statistically significant.

3 | RESULTS

After screening by the criteria of enrollment and exclusion (see Table 1), there was a total of 42 patients enrolled, and then divided

TABLE 1 Category of excluded patients before enrolling randomization

Thrombus grade less than 3	62
IRA condition not fit to PCI	12
Prior intravenous thrombolysis treatment	5
Cardiac shock	4
Refuse to enroll into study	3
Contraindication of anti-coagulation	2
Total	**88**

Abbreviations: IRA, infarct related artery; PCI, percutaneous coronary intervention.

into the two groups randomly, each group containing 21 patients. During the primary PCI, two patients in the TA group were transferred to the TCA group because the aspiration catheter failed to arrive at appropriate position to launch an aspiration, while three patients in the TCA group were eliminated from the study because the microcatheter did not reach the target thrombus and fail to perform a successful intracoronary thrombolysis. Therefore, 20 patients were enrolled in TCA group while 19 patients in TA group at last. There were no statistical differences between the two groups in clinical characteristics such as age, sex, vital signs, risk factors, GRACE, and CRUSADE scores. Laboratory tests such as CK-MB, cTnI, serum creatine, potassium, and glucose also showed no significant differences (see Table 2).

When examining imaging features related to the initial CAG and PCI, such as onset-to-balloon time (Onset-B), and first-medical-contact-to-balloon time (FMC-B) for the IRA, there was no statistical difference. The initial TIMI flow grade, CTFC, and thrombus grade showed no discrepancy between the two groups either (see Table 3) Immediately after the reperfusion therapy, angiography showed that the TCA group had more patients reaching grade 3 TIMI flow (75.0% vs. 52.6%, $p = 0.041$) and grade 3 TMPG (80.0% vs. 47.4%, $p = 0.048$), as well as a lower CTFC compared with the TA group (21.57 ± 10.18 vs. 28.59 ± 9.94 frames, $p < 0.001$). Besides there were more patients from TCA group had met a totally clearance of thrombosis (reached thrombus grade 0) after therapy (65.0% vs. 26.3%, $p = 0.025$). Through comparison of IMR results we found the TCA group had significantly lower IMR values than the TA group (29.33 ± 8.56 vs. 40.47 ± 9.35, $p < 0.001$), but there was no difference on the aspect of stent implantation (see Table 4).

In the repeat CAG 7 days later, we discovered almost all of the patients from TCA group reached TIMI grade 3, however, there is no statistical difference compared with TA group (90.0% vs. 63.2%, $p = 0.065$). The TCA group's CTFC did not differ from the TA group's (19.21 ± 9.28 vs. 22.39 ± 9.54 frames, $p = 0.162$), but did show better on TMPG, as high as 90% of those attained TMPG 3 that significantly higher than TA groups (90.0% vs. 47.4%, $p = 0.006$). Through the SPECT examination, the TCA group showed less perfusion descending areas (PDAs) than the TA group (14.4 ± 8.5% vs. 19.6 ± 3.3%, $p = 0.041$). The ST-segment restoration on ECG and the peak values of myocardial necrosis markers showed no difference between the two groups. However, by analyzing the echocardiographic outcome, we found the TCA group slightly surpassed the TA group in LVEF, although the difference did not reach criteria for statistical significance (52.4% ± 12.2% vs. 49.8% ± 11.5%, $p = 0.084$) (see Tables 5 and 6).

TABLE 2 Baseline clinical characteristics of groups

Variables	TCA group (n = 20)	TA group (n = 19)	*p* value
Age (years)	62.56 ± 11.14	63.17 ± 11.22	0.516
Male, n (%)	16(80.0)	15(78.9)	1.000
SBP (mmHg)	123.51 ± 29.38	130.46 ± 28.22	0.165
DBP (mmHg)	81.33 ± 19.213	83.78 ± 15.55	0.668
Heart rate (bpm)	83.05 ± 17.17	75.06 ± 14.57	0.129
Killip grade			0.751
Grade I, n (%)	8 (40.0)	9 (47.4)	
Grade II/III, n (%)	12 (60.0)	10 (52.6)	
History of CAD, n (%)	11 (55.0)	11 (61.1)	1.000
Hypertension, n (%)	11 (55.0)	10 (52.6)	1.000
Diabetes, n (%)	4 (20.0)	5 (26.3)	0.716
Hyperlipidemia, n (%)	9 (45.0)	9 (47.4)	1.000
Smoking, n (%)	13 (65.0)	9 (47.4)	0.341
Laboratory test on admission			
CK-MB (U/L)	126 (28, 392)	101(48, 287)	0.127
Cardiac troponin I (ng/mL)	3.30 (1.65, 18.0)	4.90 (1.35, 22.8)	0.333
Serum creatinine (μmol/L)	87.51 ± 19.21	71.09 ± 17.00	0.225
Serum potassium (mmol/L)	3.98 ± 0.56	4.15 ± 0.77	0.424
LDL cholesterol (mmol/L)	2.80(2.30, 3.34)	2.86(2.64, 3.38)	0.410
Glucose (mmol/L)	7.50(5.40, 9.61)	6.61(5.23, 7.78)	0.088
D-dimer (μg/mL)	0.14(0.08, 0.28)	0.14(0.10, 0.30)	1.000
Preprocedural medication			
DAPT, n (%)	13 (65.0)	15 (78.9)	0.480
Statins, n (%)	12 (60.0)	9 (47.4)	0.752
GRACE score	160.31 ± 37. 20	141.65 ± 35.02	0.850
CRUSADE score	31.56 ± 17.44	23.56 ± 12.99	0.098

Abbreviations: TCA, thrombolysis and anisodamine via catheter; TA, thrombus aspiration; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; CK-MB, creatine kinase-muscle/brain; LDL, low density lipoprotein; DAPT, dual antiplatelet therapy.

When a 90-day follow-up was concluded, we found no difference in incidence of MACEs or stroke. As to bleeding complications, there were no major bleeding events in either group, and no significant difference in occurrence rates of minor bleeding complications (20.0% vs. 15.8%, $p = 1.000$) between the two groups (see Table 7).

4 | DISCUSSION

In STEMI, one of the most severe and critical cardiovascular emergencies, opening the IRA without delay to rescue surviving myocardium is the most important principle in therapeutics. Due to the pathophysiologic mechanism of STEMI, the magnitude of coronary thrombus directly relates to the severity of the myocardial infarction, the risk of cardiac death, and the difficulty of reperfusion therapies, as well as the final prognosis of this disease.[11] In particular, for those with grade 3 or higher thrombus load in the IRA there is more risk of obstructing the epicardial coronary arteries by multiple thrombosis; similarly, the downstream movement of severe thrombosis may easily bring about damage to the function of the myocardial microcirculatory system and lead to deteriorating myocardial perfusion. Methods are urgently

TABLE 3 Angiographic features before PCI

Variables	TCA group (n = 20)	TA group (n = 19)	*p* value
Onset to balloon (hr)	5.5(2.5, 8.5)	5.5(3.0, 8.5)	1.000
FMC to balloon (hr)	2.0(1.0, 3.0)	1.5(1.0, 2.5)	0.156
Lesion artery number, n (%)			1.000
Single-vessel	5(25.0)	5(26.3)	
Multi-vessel	15(75.0)	14(73.7)	
TIMI flow before PCI, n (%)			0.661
0	18(90.0)	16 (84.2)	
1	2 (10.0)	3 (15.8)	
2–3	0 (0.00)	0 (0.00)	
Thrombus score Before PCI, n (%)			0.407
0–2	0(0.00)	0(0.00)	
3–4	2(10.0)	4(21.1)	
5	18(90.0)	15 (78.9)	
CTFC before PCI, frames	38.54 ± 6.78	42.82 ± 9.28	0.382

Abbreviations: TCA, thrombolysis and anisodamine via catheter; TA, thrombus aspiration; FMC, first medical contact; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention; CTFC, corrected TIMI Frame count.

needed in cases with high thrombus loads to simultaneously re-open the IRA and prevent the microcirculation from being damaged by either the existing thrombosis or by subsequent thrombus debris and other micromaterials after interventional treatment. This may be one of the greatest challenges in performing primary PCI operations. Intracoronary thrombus aspiration is a commonly used technique to deal with high thrombus loads, and surely achieves good outcomes in some primary PCI cases. But due to its mechanism, it inevitably exerts a physical and mechanical compression and disintegration force onto the thrombosis and plaques, which can generate a considerable amount of thrombus debris and other micro-fragments. Unavoidably, these effects are likely to damage the myocardial microcirculation and affect myocardial perfusion.

Since the 1980s, directly injecting thrombolytic medicine via catheters into coronary arteries has been undertaken, and its feasibility has been verified through serial studies.[12,13] In clinical practice, selective intracoronary thrombolysis has been an effective method to treat high thrombus loads in coronary arteries. Particularly after the appearance of today's new generation of highly selective thrombolytics, intracoronary thrombolysis is found more and more to have vessel-opening benefits and to show high safety.[5,11–14] In this study, for STEMI patients with grade 3 or higher thrombus load, after treating by targeted intracoronary thrombolysis combined with anisodamine, the thrombosis in epicardial arteries significantly reduced or even completely disappeared in quite a short time, with an obvious increase of antegrade TIMI flow grade and improvement on myocardial perfusion. Moreover, the change on angiography values for the CAG immediately after this combinative therapy and for the repeat CAG 7 days later both indicated a significant improvement on myocardial microcirculatory function and perfusion level. Especially notable were findings on IMR assessment, whose mechanism is most suitable to explore the coronary system's actual, physical environment, and

TABLE 4 Comparison of TIMI blood flow, myocardial perfusion and microcirculation resistance parameters during CAG and PCI between the two groups

Variables	TCA group (n = 20)	TA group (n = 19)	*p* value
TIMI flow after PCI, n (%)			
0	0(0.00)	3(15.8)	0.106
1	1(5.0)	2(10.5)	0.605
2	2(10.0)	2(10.5)	1.000
3	17(85.0)	10(52.6)	**0.041**
TMPG flow after PCI, n (%)			
0	0(0)	3(15.8)	0.106
1	1(5.0)	3(15.8)	0.342
2	3(15.0)	4(21.1)	0.695
3	16(80.0)	9(47.4)	**0.048**
Thrombus grade after PCI, n (%)			
0	13(65.0)	5(26.3)	**0.025**
1	1(5.0)	2(10.5)	0.605
2	3(15.0)	5(26.3)	0.451
3	2(10.0)	4(21.1)	0.407
4–5	1(5.0)	3(15.8)	0.342
CTFC after PCI, (frames)	21.57 ± 10.18	28.59 ± 9.94	**<0.001**
IMR after PCI, (U)	29.33 ± 8.56	40.47 ± 9.35	**<0.001**
Stents, n (%)			
0	5(25.0)	2(10.5)	0.407
1	14(70.0)	12(63.2)	0.741
≥2	1(5.0)	5(26.3)	0.091

Bold indicates $p < 0.05$.
Abbreviations: TCA, thrombolysis and anisodamine via catheter; TA, thrombus aspiration; TIMI, thrombolysis in myocardial infarction; CAG, coronary artery angiography; PCI, percutaneous coronary intervention; TMPG, TIMI myocardial perfusion grade; CTFC, corrected TIMI Frame count; IMR, index of microcirculatory resistance.

which has been validated as among the most accurate and comprehensive of recent invasive measuring techniques for myocardial microcirculatory function.[15–17] The IMR significantly demonstrated improved perfusion restoration and function preservation in the myocardial microcirculation.

In the TA group, even customary thrombus aspiration rapidly cleared the severe thrombosis and re-opened the IRA. However, comparing with the TCA group, there were still many residual thrombosis in the arteries after aspiration was performed, and longer perfusion time and lower perfusion level. To explain these results, we hypothesize that aspiration's mechanical and physical squeezing and dismembering of the thrombosis might cause secondary generation of micro-debris to obstruct the prearteriolar and arteriolar vessels, which then affects the perfusion of entire microcirculation system. In addition, the vacuum suction mechanism briefly decreases the volume of perfused blood flow and depresses the perfusion pressure in microcirculation, which may separately damage the microstructure and microvascular endothelial function. By contrast, we think the thrombolysis strategy showed advantages compared with thrombus aspiration, probably on account of the following reasons: first, entry via micro-catheter or other inventive techniques can reach deeper and as nearly as possible reach the thrombosis in the IRA, and thus

TABLE 5 Intergroup comparison of TIMI blood flow, myocardial perfusion and microcirculation resistance parameters in re-CAG after 7 days

Variables	TCA group (n = 20)	TA group (n = 19)	*p* value
TIMI flow in re-CAG, n (%)			
0	0(0.00)	1(5.3)	0.487
1	1(5.0)	1(5.3)	1.000
2	1(5.0)	5(26.3)	0.091
3	18(90.0)	12(63.2)	0.065
TMPG flow in re-CAG, n (%)			
0	0(0)	2 (10.5)	0.231
1	1(5.0)	2(10.5)	0.605
2	1(5.0)	4(21.1)	0.182
3	18(90.0)	9(47.4)	**0.006**
Thrombus grade In re-CAG, n (%)			
0	15(75.0)	12(63.2)	0.501
1	2(10.0)	3(15.8)	0.661
2	1(5.0)	2(10.5)	0.605
3	1(5.0)	2(10.5)	0.605
4–5	0(0)	0(0)	…
CTFC in re-CAG (frames)	19.21 ± 9.28	22.39 ± 9.54	0.162

Bold indicates $p < 0.05$.
Abbreviations: TCA, thrombolysis and anisodamine via catheter; TA, thrombus aspiration; re-CAG, repeat CAG; TIMI, thrombolysis in myocardial infarction; TMPG, TIMI myocardial perfusion grade; CTFC, corrected TIMI frame count.

the injection of thrombolytic medicine can easily reach a considerable local concentration and make full-scale contact with the surface of the thrombosis. In some of our cases, we even directly stabbed into the core area of thrombosis and performed a thrombolysis, resulting in rapid and effective disintegration and "melting" of the heavy thrombus load. Second, intracoronary targeted injection can ablate not only the gross thrombosis in epicardial vessels, but the thrombolytic particles can also readily reach the most microscopic parts of the structure of the coronary circulatory system, and then utterly melt down all micro thrombosis and debris. This characteristic

TABLE 6 Comparison of ECG features, myocardial necrosis markers and other features between two groups

Variables	TCA group (n = 20)	TA group (n = 19)	*p* value
STR, n (%)			
None	1(5.0)	3(15.8)	0.342
Partial	4(20.0)	2(10.5)	0.661
Complete	15(75.0)	14(73.7)	1.000
Peak CK-MB (U/L)	223(146, 311)	233(151, 369)	0.311
Peak cTnI (ng/mL)	71(59,99)	83(61, 92)	0.148
LVEF, %	52.4 ± 12.2	49.8 ± 11.5	0.084
SPECT PDA, %	14.4 ± 8.5	19.6 ± 3.3	**0.041**

Bold indicates $p < 0.05$.
Abbreviations: ECG, electrocardiography; TCA, thrombolysis and anisodamine via catheter; TA, thrombus aspiration; STR, ST-segment restoration; CK-MB, creatine kinase-muscle/brain; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction; SPECT, single photon emission computed tomography; PDA, perfusion defect area.

TABLE 7 MACEs and bleeding complications at 90-day follow-up

Variables	TCA group (n = 20)	TA group (n = 19)	*p* value
MACEs, n (%)			
Cardiac death	0 (0)	0 (0)	…
Reinfarction	0(0)	1(5.3)	0.487
Heart failure	3(15.0)	3(15.8)	1.000
TVR	0 (0)	0 (0)	…
Malignant arrhythmia	0 (0)	2(10.5)	0.231
Stroke	0 (0)	0 (0)	…
Bleeding complication, n (%)			
Major bleeding	0 (0)	0 (0)	…
Minor bleeding	4 (20.0)	3 (15.8)	1.000

Abbreviations: MACE, major adverse cardiovascular events; TCA, thrombolysis and anisodamine via catheter; TA, thrombus aspiration; TVR, target vessel revascularization.

may eventually achieve a permeating clearance to the thrombosis, extending from the conductive vessels to the arteriolar vessels.

Another explanation for our good outcomes is that we chose the third-generation highly selective thrombolytic pro-urokinase as our intracoronary thrombolytic medicine. Compared with the older generation thrombolytics, like urokinase and streptokinase, it does not conjugate with plasma prothrombin, which avoids the dose waste before contact with the thrombosis, and refrains from stimulating the coagulatory system to produce additional thrombus before performing its anti-thrombotic effect, as well as reducing the incident rate of bleeding events. Therefore, we selected this drug for its more effective thrombus ablation and higher safety profile.

The intracoronary use of microcirculation-improving medicine like nitroprusside and nicorandil has been developed to prevent and treat the slow-flow or no-flow reperfusion phenomenon and been in use for many years. *Scopolia tangutica* is an effective traditional herb that has been widely used in frostbite and shock treatment by local residents in the Tibet area of China for at least hundreds of years. Its extract, anisodamine, has been proven to have multiple microcirculation-improving and preventive effects by our team's research over 20 years. Anisodamine can raise perfusion pressure and lower the resistance of myocardial microcirculation, prevent endothelial injury and ischemia reperfusion injury, and improve electrophysiologic stability.[7–9] By comparing sequential angiographies, SPECT imaging, and follow-up outcome measures, this study shows that combining this medicine with targeted intracoronary thrombolysis in patients with STEMI, while safe, confers advantages not only on the efficacy of opening IRAs with high thrombus loads, but also on the indicators of microcirculation, which also indicates a better prognosis.

5 | CONCLUSION

In primary PCI for STEMI patients with a high thrombus load, both of the two strategies included achieved a satisfactory effect on opening IRA and reducing thrombus loads. Compared with standard thrombus aspiration, the strategy of intracoronary targeted intracoronary thrombolysis combined with anisodamine injection, via catheter, can more quickly and effectively clear the thrombosis and restore myocardial

perfusion, and it has additional benefits of preventing deterioration and improving function in the myocardial microcirculation, increasing the level of myocardial reperfusion, decreasing the area of infarction, and further meliorating the prognosis.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGMENTS

We thank Hong-Ming Zheng and Hong-Ning Yin for their assistance with SPECT and Echocardiography technique, and Qing Miao, Chen Liu, Yan-Bo Wang, Wei Li, Wei Zhi, Yi Li, Qing Wang, Xiang-Ming Li and Qian Zhang for their great help in this study.

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How to cite this article: Fu Y, Gu X-S, Hao G-Z, et al. Comparison of myocardial microcirculatory perfusion after catheter-administered intracoronary thrombolysis with anisodamine versus standard thrombus aspiration in patients with ST-elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2019;93:839–845. https://doi.org/10.1002/ccd.28112