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CLINICAL TRIAL REPORT

Number of Retrieval Attempts and the Association of Intravenous Tirofiban with Symptomatic Intracranial Hemorrhage in Patients with Successful Endovascular Therapy: Results of the RESCUE BT Trial

Xiangxiang Peng[1,*], Changwei Guo[2,*], Jie Yang[2], Shitao Fan[2], Xu Xu[2], Jinfu Ma[2], Zhixi Wang[2], Shihai Yang[2], Wenjie Zi[2], Xianjun Huang[1], Hongjun Wang[3]

[1]Department of Neurology, Yijishan Hospital of Wannan Medical College, Wuhu, Anhui Province, People's Republic of China; [2]Department of Neurology, Xinqiao Hospital and The Second Affiliated Hospital, Army Medical University (Third Military Medical University), Chongqing, People's Republic of China; [3]Department of Neurology, Chongqing Fengdu People's Hospital, Chongqing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xianjun Huang, Department of Neurology, Yijishan Hospital of Wannan Medical College, No. 92 Zheshan Road, Wuhu, Anhui Province, 241000, People's Republic of China, Tel +86-553-5739543, Email doctorhuangxj@hotmail.com; Hongjun Wang, Department of Neurology, Chongqing Fengdu People's Hospital, No. 214, West Section of Pingdu Avenue, Sanhe Town, Fengdu County, Chongqing, 408200, People's Republic of China, Email whj13364012222@163.com

Purpose: To investigate the relationship between intravenous tirofiban, the number of retrieval attempts and symptomatic intracranial hemorrhage (sICH) in patients with successful EVT.

Patients and Methods: We used the data from the Endovascular Treatment With versus Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) Trial. The primary outcome was sICH, which was defined according to the Heidelberg Bleeding Classification. The association between the number of retrieval attempts and the rate of sICH was investigated using multivariable logistic regression.

Results: A total of 866 patients were included in our analysis. In overall cohort, tirofiban (OR: 1.853, 95% CI: 1.039–3.307) and more than 2 passes (3 versus 0–1: OR: 2.482, 95% CI: 1.124–5.481; 2 versus 0–1: OR: 0.813, 95% CI: 0.389–1.696) were significantly associated with the occurrence of sICH. A significant interaction between the use of tirofiban and the increasing number of attempts was found (p for interaction = 0.02), whereby the presence of sICH was significantly associated with tirofiban (OR: 5.534, 95% CI: 1.586–19.315) in the subgroup of multiple passes (>2 passes group), while none was seen in the subgroup of 0–2 passes. The results of the sensitivity analysis also showed that more than 2 passes (3 versus 1: OR: 2.841, 95% CI: 1.102–7.323; 2 versus 1: OR: 0.852, 95% CI: 0.346–2.097) were significantly associated with the occurrence of sICH in the tirofiban group but not in the placebo group.

Conclusion: In patients with multiple attempts, intravenous tirofiban may increase the risk of sICH. Further research and individualized risk assessment are necessary to determine the most appropriate strategy of intravenous tirofiban for EVT patients, especially considering details of thrombectomy procedures.

Registration: : URL: http:// www.chictr.org.cn; Unique identifier: ChiCTR-INR-17014167.

Keywords: tirofiban, hemorrhage, endovascular treatment, stroke

Introduction

Endovascular therapy (EVT) has been established as the standard for treatment of acute large-vessel occlusion stroke, regardless of whether the stroke is an anterior circulation or a posterior circulation stroke.[1–3] Successful reperfusion is the most important modifiable predictor of good clinical outcome.[4] Studies have reported that achieving complete revascularization after a single device pass, called the first pass effect (FPE),[5] is associated with favorable clinical outcomes; however, the

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proportion of FPE in the real world is less than one-third.[6,7] Hence, more than one pass is often needed in clinical practice to achieve successful reperfusion.

Importantly, an increase in the number of device passes will inevitably lead to endothelial damage or/and plaque disruption, which may further result in platelet activation, aggregation and subsequent thrombosis. At this time, one approach is to pharmacologically prevent the aggregation of platelets.[8] In clinical practice, tirofiban, as a glycoprotein IIb/IIIa antagonist, is predominantly used to prevent thromboembolic complications and is an adjunctive treatment for EVT.[9,10] Therefore, multiple retrieval attempts during EVT are the most common usage scenario for tirofiban. However, regardless of the increasing number of passes and the use of tirofiban, one of the major concerns is the complication of intracranial hemorrhage (ICH).

Studies have observed an association between the number of retrieval attempts and symptomatic intracranial hemorrhage (sICH).[11,12] However, most studies recommended that in cases of persistent occlusion, at least 3 retrieval attempts were should be performed.[13,14] Additionally, the safety and effectiveness of tirofiban as an adjunct to EVT has also been controversial in previous observational studies.[10,15,16] One possible explanation is that previous studies have overlooked the interaction between the details of thrombectomy procedures and the safety and effectiveness of tirofiban. We hypothesize that tirofiban may increase the risk of sICH in patients with multiple retrieval attempts of EVT.

To test this hypothesis, we investigated the relationship between tirofiban, the number of retrieval attempts and sICH using data from the Endovascular Treatment With versus Without Tirofiban for Patients with Large Vessel Occlusion Stroke (RESCUE BT) Trial, a multicenter, randomized, placebo-controlled, double-blind clinical trial.

Materials and Methods

Patients Selection

We analyzed the data of patients with acute ischemic stroke who were enrolled in the RESCUE BT trial. The RESCUE BT trial is an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial in ischemic stroke patients within 24 hours of stroke onset from October 10, 2018, to October 31, 2021, with recruitment from 55 centers in China.[17] This trial was registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn; ChiCTR-INR-17014167). The trial protocol was previously published and approved by the medical ethics committees of Xinqiao Hospital and all participating hospitals.[18] Written informed consent was provided by each patient or their legal representative.

In the RESCUE BT trial, a total of 948 consecutive patients were recruited and were randomly assigned a 1:1 ratio to receive intravenous tirofiban or placebo treatment before EVT. The inclusion criterion were as follows:[18] (1) patients presenting with acute ischemic stroke within 24 hours of the last known wellness; (2) the National Institutes of Health Stroke Scale (NIHSS) score of 30 or less at admission; (3) the Alberta Stroke Program Early CT Score (ASPECTS) value of 6 to 10, and (4) occlusion of the intracranial internal carotid artery (ICA) or the M1 or M2 segment of the middle cerebral artery (MCA) confirmed by computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography. In the present study, we excluded the patients with final Expanded Thrombolysis in Cerebral Infarction (eTICI) following angiography 0–2a (The flowchart for the study population is shown in Figure S1).

Variable Definition

The clinical, radiological and therapeutic characteristics of patients were collected prospectively. All imaging data were adjudicated by an independent Imaging Core Laboratory, with the staff unaware of the treatment assignment. The number of retrievals included both aspiration attempts and retrievals with stent retriever devices. Multiple passes were defined as the number of retrievals more than 2. The patients were dichotomized into 0–2 device passes and >2 passes groups.

The adjudication of ICH was determined by the Imaging Core Laboratory based on follow-up CT within 24 h after stopping tirofiban treatment. sICH was assessed by the Heidelberg Bleeding Classification.[19] sICH was diagnosed if the newly observed ICH on follow-up images accompanied by any of the following conditions: (1) the NIHSS score increased more than 4 points or more than 2 points in one category; (2) deterioration led to endotracheal intubation, decompressive craniectomy, external ventricular drain placement or any other major interventions; and (4) neurological deterioration could not be explained by reasons other than the detected ICH.

Statistical Analysis

Continuous variables were expressed as medians (interquartile range, IQR) and analyzed using the Mann–Whitney *U*-test. Categorical variables are presented as percentages and were analyzed using the chi-square test or Fisher's exact test as appropriate. Baseline characteristics and treatment-related characteristics were compared between the tirofiban and placebo groups or between the sICH and non-sICH groups. The primary outcome of interest was sICH. The association between the number of retrieval attempts and the rate of sICH was investigated separately in the tirofiban and control groups using multivariable logistic regression. Furthermore, the association between the usage of tirofiban and the rate of sICH was further investigated in the multiple retrieval attempts group.

A sensitivity analysis was also performed, accounting for only patients with stent retriever devices and/or aspiration attempts and excluding patients with the use of balloon angioplasty and/or stenting.

All variables with p values <0.1 in the univariate analysis were included in the multivariate analysis. ORs and 95% CIs were calculated. For all analyses, a two-tailed value of $p \leq 0.05$ was considered significant. All statistical analyses were performed using the SPSS software package.

Results

Baseline Characteristics

Among 948 patients enrolled in the RESCUE BT trial cohort, 3 patients were excluded due to missing data on sICH, and 79 patients were excluded due to a final eTICI grade of 0–2a. A total of 866 patients were included in our analysis. The baseline and procedural characteristics are provided in Table S1.

The baseline characteristics, including age, sex, medical history, medication history, baseline NIHSS score and ASPECT score, stroke etiology, occlusion site, collateral circulation status, workflow metrics and treatment-related characteristics were well balanced between the tirofiban and placebo groups. However, the tirofiban group had a higher rate of sICH (9.4% versus 5.2%, $p = 0.019$). Additionally, in the characteristics of EVT, the tirofiban group had fewer number of passes (1 versus 2; $p = 0.054$), although it did not reach statistical significance.

Predictors of sICH in the Overall Cohort

In the univariate analyses, the factors associated with sICH versus non-sICH were prior antiplatelet history (17.5% versus 9%, $p = 0.027$), baseline ASPECT score (7 versus 8, $p < 0.001$), occlusion site (ICA, 36.5% versus 19.4%, MCA M1, 49.2% versus 67.2%, MCA M2, 14.3% versus 13.3%, $p = 0.004$), poor collateral circulation status (44.4% versus 28.6%, $p = 0.008$) and high baseline serum glucose (7.5 mmol/l versus 6.88 mmol/l, $p = 0.007$). Additionally, age, the rate of atrial fibrillation and smoking, baseline NIHSS score, and the number of passes in the sICH group were higher than those in the non-sICH group, although the differences did not reach statistical significance. Baseline characteristics of the overall cohort stratified by the occurrence of sICH are shown in Table 1.

The multivariable logistic regression analyses revealed that tirofiban (OR: 1.853, 95% CI: 1.039–3.307, $p = 0.027$) and more than 2 passes (3 versus 0–1: OR: 2.482, 95% CI: 1.124–5.481, $p = 0.024$; 2 versus 0–1: OR: 0.813, 95% CI: 0.389–1.696, $p = 0.580$) were significantly associated with the occurrence of sICH. A significant interaction between the use of tirofiban and the increasing number of attempts was found (p for interaction = 0.02, Figure 1). Additionally, high baseline serum glucose and ASPECT score were related to the development of sICH. Interestingly, we found that prior antiplatelet history (OR: 2.844, 95% CI: 1.330–6.617, $p = 0.007$) was also significantly associated with sICH after EVT. Predictors of symptomatic intracranial hemorrhage for overall cohort are shown in Table 2

Predictors of sICH in Patients with Multiple Retrieval Attempts (>2 Passes)

After adjusting for factors with $p < 0.1$ in the univariate analyses (Table 3), the presence of sICH was significantly associated with tirofiban (OR: 5.534, 95% CI: 1.586–19.315, $p = 0.007$). Additionally, prior antiplatelet history (OR: 11.392, 95% CI: 2.749–47.212, $p = 0.001$) was also significantly associated with sICH after EVT. Predictors of sICH in patients with multiple passes (>2 passes) are shown in Table 4. However, in patients with 0–2 passes, there were no

Table 1 Baseline Characteristics of the Overall Cohort Stratified by the Occurrence of sICH

	No-sICH	sICH	P value
N	803	63	
Age, median (IQR), years	67(57,74)	70(63,74)	0.079
Men, n (%)	473(58.9)	36(57.1)	0.784
Tirofiban, n (%)	387 (48.2)	40(63.5)	0.019
Medical history, n (%)			
Hypertension	443(55.2)	30(47.6)	0.246
Atrial fibrillation	260(32.4)	27(42.9)	0.089
Coronary heart disease	131(16.3)	13(20.6)	0.375
Diabetes mellitus	168(20.9)	14(22.2)	0.807
Hyperlipidemia	113(14.1)	7(11.1)	0.512
Ischemic stroke	134(16.7)	13(20.6)	0.422
Current smoking	192(23.9)	9(14.3)	0.081
Pre-stroke modified Rankin scale, n (%)			0.698
0	734(91.4)	57(90.5)	
1	47(5.9)	5(7.9)	
>2	22(2.7)	1(1.6)	
Prior antithrombotic drug use, n (%)			
Antiplatelet	72(9)	11(17.5)	0.027
Direct oral anticoagulant	62(7.7)	7(11.1)	0.339
Clinical characteristics			
Baseline NIHSS score, median (IQR)	16(12,19)	17(12,21)	0.064
Baseline ASPECTS, median (IQR)	8(7,9)	7(6,8)	<0.001
Systolic blood pressure, median (IQR)	145(129,160)	147(130,168)	0.532
Diastolic blood pressure, median (IQR)	84(75,94)	84(75,93)	0.619
Stroke etiology, n (%)			0.203
LAA	359(44.7)	23(36.5)	
CE	357(44.5)	29(46)	
Other or unknown	87(10.8)	11(17.5)	
Radiological characteristics, n (%)			
Occlusion site			0.004
ICA	156(19.4)	23(36.5)	
MCA M1	540(67.2)	31(49.2)	
MCA M2	107(13.3)	9(14.3)	
ASITN/SIR[a]			0.008
0–1	229(28.6)	28(44.4)	
2–4	573(71.4)	35(55.6)	
Workflow times, median (IQR), min			
Time from onset to randomization	396(253,630)	401(302,619)	0.577
Time from onset to puncture	390(250,634)	395(267,640)	0.635
Puncture to reperfusion or procedure completion	65(40,100)	64(40,100)	0.915
Treatment-related characteristics			
Intravenous alteplase treatment, n (%)	16(2)	1(1.6)	0.823
Intraarterial thrombolysis, n (%)	23(2.9)	2(3.2)	0.887
Intraarterial tirofiban, n (%)	61(7.6)	3(4.8)	0.408
Firstline EVT, n (%)			0.407
Stent retriever	218(27.1)	14(22.2)	
Aspiration	319(39.7)	27(42.9)	
Combined stent retriever and aspiration	178(22.2)	18(28.6)	
Other	88(11)	4(6.3)	

(*Continued*)

Table 1 (Continued).

	No-sICH	sICH	P value
Number of passes, n (%)	1(1,2)	2(1,3)	0.085
0–1, n. (%)	409(50.9)	28(44.4)	
2, n. (%)	232(28.9)	14(22.2)	
3, n. (%)	91(11.3)	13(20.6)	
>3, n. (%)	71(8.8)	8(12.7)	
General anesthesia, n (%)	258(32.1)	23(36.5)	0.475
Laboratory Test			
Serum glucose[b], median (IQR), mmol/l	6.88(5.72,8.51)	7.50(6.24,10.60)	0.007

Notes: [a]Data were not available for 1 patient. [b]Data were not available for 58 patients (5 in the sICH group and 53 in the non-sICH group).

Abbreviations: ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECT, Alberta Stroke Program Early CT; CE, cardioembolism; EVT, endovascular therapy; eTICI, Expanded Thrombolysis in Cerebral Infarction; ICA, internal carotid artery; LAA, large artery atherosclerosis; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; sICA, symptomatic intracranial hemorrhage.

significant differences in the occurrence of sICH between the tirofiban and placebo groups in the univariate analyses (details are provided in online-only Table S2).

Predictors of sICH Separately in the Tirofiban and Placebo Groups

The baseline and procedural characteristics between the sICH versus non-sICH groups in the tirofiban and placebo groups are shown in Table S3. A multivariable logistic regression model using factors with $p < 0.1$ in the univariate analyses showed that more than 2 passes (3 versus 0–1: OR: 3.528, 95% CI: 1.375–9.054, $p = 0.009$; 2 versus 0–1: OR: 0.941, 95% CI: 0.383–2.311, $p = 0.895$) were significantly associated with the occurrence of sICH in the tirofiban group but not in the placebo group.

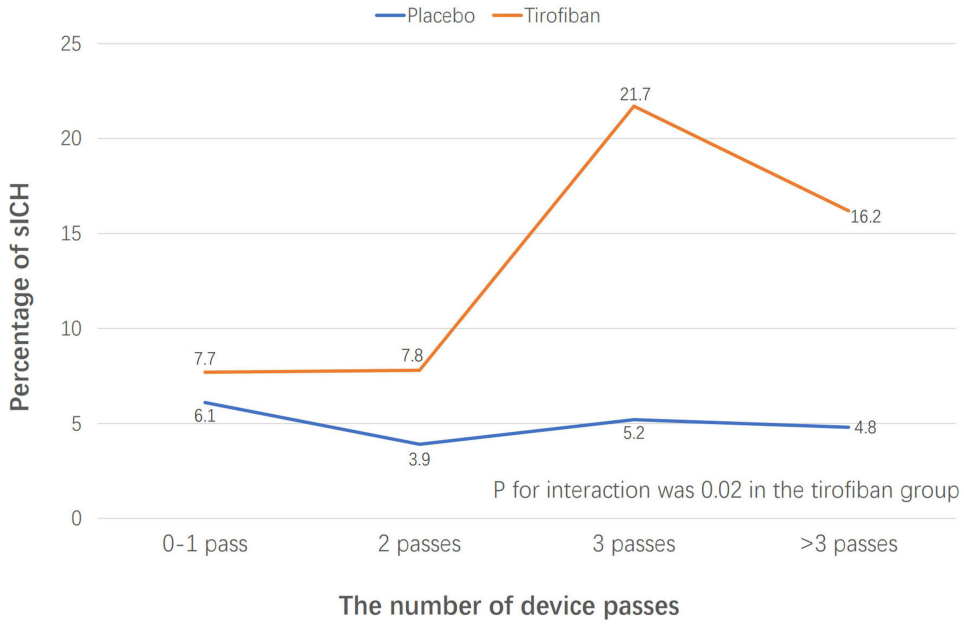

Figure 1 Relative frequencies of symptomatic intracranial hemorrhage by the number of retrieval attempts. The *p* value for interaction between the use of tirofiban and the increasing number of attempts was 0.02.

Table 2 Predictors of Symptomatic Intracranial Hemorrhage for Overall Cohort (n = 866)

	OR	95% CI	P value
Tirofiban	1.853	1.039–3.307	0.037
Age	1.014	0.986–1.043	0.334
Atrial fibrillation	1.163	0.641–2.109	0.619
Current smoking	0.735	0.333–1.625	0.447
Previous Antiplatelet	2.864	1.330–6.167	0.007
Baseline NIHSS score	1.007	0.633–0.876	0.826
Baseline ASPECTS	0.744	0.633–0.876	<0.001
Occlusion site			
ICA	1.284	0.535–3.081	0.576
MCA M1	0.541	0.236–1.243	0.148
MCA M2		Reference	
ASITN/SIR			
0–1		Reference	
2–4	0.606	0.328–1.121	0.110
Number of passes			
0–1		Reference	
2	0.813	0.389–1.696	0.580
3	2.482	1.124–5.481	0.024
>3	1.417	0.556–3.606	0.465
Serum glucose	1.117	1.044–1.196	0.001

Abbreviations: ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECT, Alberta Stroke Program Early CT; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

Table 3 Baseline Characteristics of the Patients with Multiple Passes (>2 Passes) Stratified by sICH

	No-sICH	sICH	P value
N	162	21	
Tirofiban	67(41.4)	16(76.2)	0.003
Age, median (IQR), years	67(57,74)	73(66,76)	0.030
Men, n (%)	89(54.9)	14(66.7)	0.308
Medical history, n (%)			
Hypertension	73(45.1)	9(42.9)	0.848
Atrial fibrillation	58(35.8)	11(52.4)	0.140
Coronary heart disease	25(15.4)	5(23.8)	0.329
Diabetes mellitus	22(13.6)	2(9.5)	0.604
Hyperlipidemia	19(11.7)	2(9.5)	0.766
Ischemic stroke	32(19.8)	4(19)	0.939
Current smoking	34(21)	3(14.3)	0.472
Pre-stroke modified Rankin scale, n (%)			0.818
0	143(88.3)	19(90.5)	
1	16(9.9)	2(9.5)	
>2	3(1.9)	0	
Prior antithrombotic drug use, n (%)			
Antiplatelet	13(8)	6(28.6)	0.004
Direct oral anticoagulant	13(8)	2(9.5)	0.814

(*Continued*)

Table 3 (Continued).

	No-sICH	sICH	P value
Clinical characteristics			
Baseline NIHSS score, median (IQR)	16(13,20)	17(16,21)	0.163
Baseline ASPECTS, median (IQR)	8(7,9)	6(6,8)	0.017
Systolic blood pressure, median (IQR)	145(126,160)	147(131,170)	0.314
Diastolic blood pressure, median (IQR)	82(74,93)	84(74,98)	0.741
Stroke etiology, n (%)			0.057
LAA	64(39.5)	4(19)	
CE	87(53.7)	13(61.9)	
Other or unknown	11(6.8)	4(19)	
Radiological characteristics, n (%)			
Occlusion site			0.017
ICA	40(24.7)	10(47.6)	
MCA M1	106(65.4)	7(33.3)	
MCA M2	16(9.9)	4(19)	
ASITN/SIR			0.267
0–1	43(26.5)	8(38.1)	
2–4	119(73.5)	13(61.9)	
Workflow times, median (IQR), min			
Time from onset to randomization	367(240,567)	424(336,647)	0.172
Time from onset to puncture	377(222,581)	395(330,648)	0.196
Puncture to reperfusion or procedure completion	89(57,126)	78(62,133)	0.825
Treatment-related characteristics			
Intravenous alteplase treatment, n (%)	4(2.5)	1(4.8)	0.544
Intraarterial thrombolysis, n (%)	4(2.5)	0	0.467
Intraarterial tirofiban, n (%)	12(7.4)	1(4.8)	0.657
Firstline EVT, n (%)			0.759
Stent retriever	43(26.5)	4(19)	
Aspiration	85(52.5)	12(57.1)	
Combined stent retriever and aspiration	34(21)	5(23.8)	
Number of passes, n (%)	3(3,4)	3(3,4)	0.711
General anesthesia, n (%)	44(27.2)	5(23.8)	0.744
Laboratory Test			
Serum glucose, median (IQR), mmol/l	6.70(5.62,8.11)	7.10(6.33,8.65)	0.205

Abbreviations: ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECT, Alberta Stroke Program Early CT; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

Additionally, age was significantly associated with sICH in the tirofiban group, while prior antiplatelet history, baseline serum glucose and ASPECT score were related to the development of sICH in the placebo group. Figure 2A and B show the results of the multivariable logistic regression analyses in the tirofiban and placebo groups.

Sensitivity Analysis

Considering the differences in different EVT approaches, we excluded patients with the use of balloon angioplasty and/or stenting only and performed a sensitivity analysis. The baseline and procedural characteristics between the sICH versus non-sICH groups in the tirofiban and placebo groups are shown in Table S4. The results of the sensitivity analysis also showed that more than 2 passes (3 versus 1: OR: 2.841, 95% CI: 1.102–7.323, $p = 0.031$; 2 versus 1: OR: 0.852, 95% CI: 0.346–2.097, $p = 0.728$) were significantly associated with the occurrence of sICH in the tirofiban group but not in the placebo group (Figure 2C and D).

Table 4 Predictors of sICH in Patients with Multiple Passes (>2 Passes)

	OR	95% CI	P value
Tirofiban	5.534	1.586–19.315	0.007
Age	1.048	0.991–1.109	0.100
Previous Antiplatelet	11.392	2.749–47.212	0.001
Baseline ASPECTS	0.748	0.537–1.042	0.086
Occlusion site			
ICA	0.976	0.192–4.968	0.977
MCA M1	0.165	0.033–0.833	0.029
MCA M2		Reference	
Stroke etiology			
LAA		Reference	
CE	1.210	0.310–4.722	0.075
Other or unknown	2.417	0.366–15.949	0.840

Abbreviations: ASPECT, Alberta Stroke Program Early CT; CE, cardioembolism; ICA, internal carotid artery; LAA, large artery atherosclerosis; MCA, middle cerebral artery; sICA, symptomatic intracranial hemorrhage.

Discussion

In the present study, we investigated that the relationship between tirofiban, the number of retrieval attempts and the occurrence of sICH. Our study demonstrated three main findings. First, tirofiban and more than 2 passes were significantly

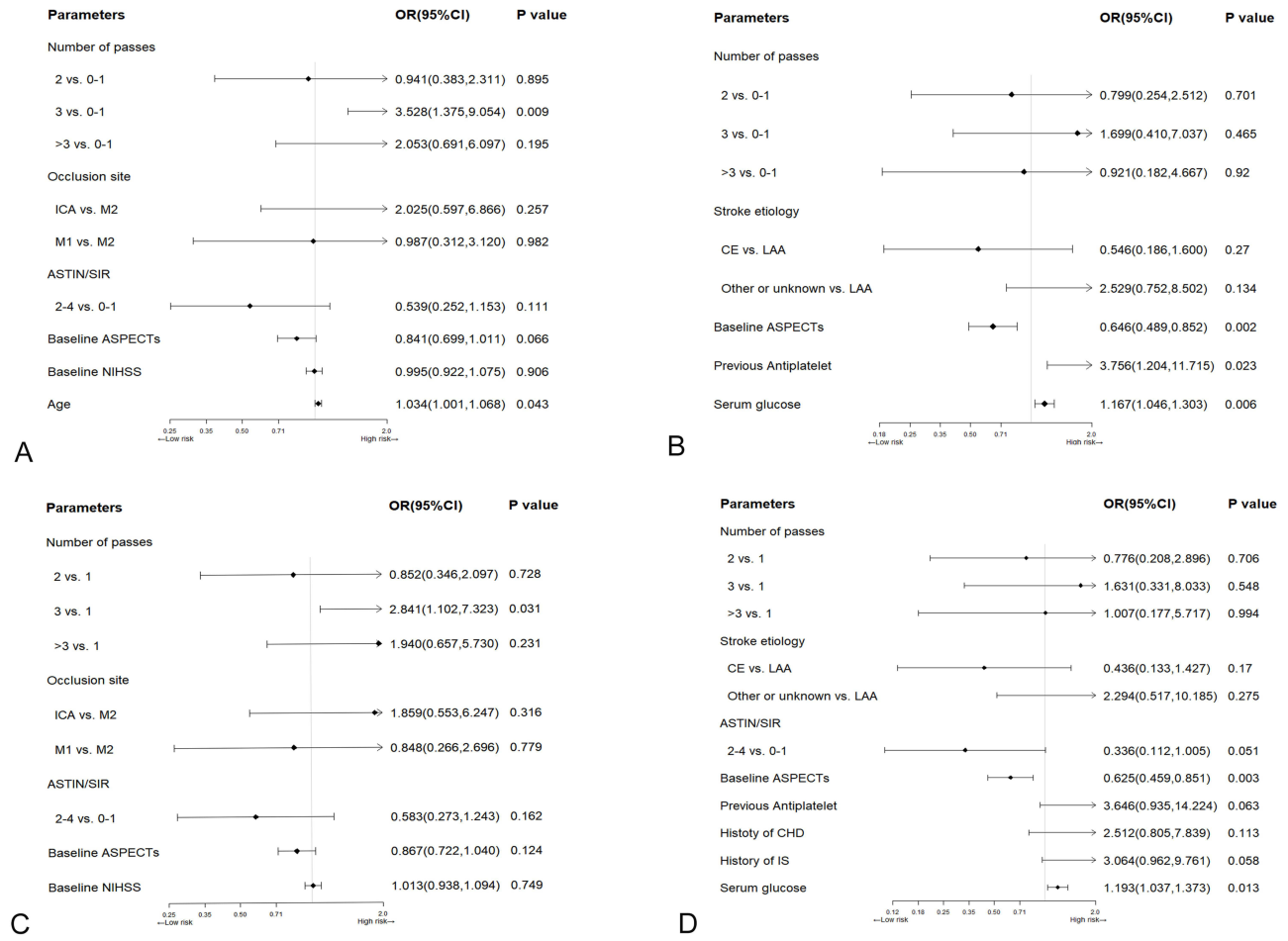

Figure 2 Odds ratios (ORs) for the development of symptomatic intracranial hemorrhage (**A** and **B**) in all enrolled patients (n = 866), and (**C** and **D**) in patients in the sensitivity analysis (n = 774). (**A** and **C**) are the tirofiban groups; (**B** and **D**) are the placebo groups.

associated with the occurrence of sICH. Second, the association of tirofiban with the risk of sICH only be seen in patients with multiple passes (>2 passes). This suggests that the association of sICH and the tirofiban was modified by the number of attempts. Third, prior antiplatelet history may also be associated with a higher risk of sICH in EVT patients, especially in multiple passes patients.

A direct association between the number of retrieval attempts and the occurrence of sICH has been assessed in several previous studies.[11,12,20] Earlier, a multicenter registry study from China (ACTUAL Registry)[12] showed that more than 3 passes was associated with an increased risk of sICH. However, an important drawback of the ACTUAL Registry study was the significantly higher sICH rate compared to ours (17.2% vs 7.3%). This discrepancy may be attributed to differences in the time windows used for sICH evaluation (within 72 hours vs within 24 hours). The longer time window in the ACTUAL study may have captured later occurrences of sICH that were missed in our 24-hour window, which could also explain why no significant correlation was observed between the number of passes and sICH occurrence in the placebo group in our study. Additionally, the differences may be due to the limited thrombectomy technology and equipment available during the early era of EVT. A recent study by Maros et al[11] also indicated that the likelihood of sICH was increased after more than 3 passes during EVT, regardless of age, baseline NIHSS, or procedure time. Our findings were partly in accordance with the results of these studies. In the present study, we found that more than 2 passes during EVT were significantly associated with the occurrence of sICH.

In clinical practice, more than one pass is often needed to achieve successful reperfusion, despite FPE described as a metric of technical success for EVT.[4,14,21] A large multicentric register study by Flottmann et al[14] showed that at least 3 retrieval attempts should be performed in endovascular therapy. Baek et al[21] recommend that successful recanalization should be achieved within 4 passes of a stent retriever. However, an increase in the number of device passes will lead to endothelial damage or/and plaque disruption, resulting in thrombotic complications. In this context, periprocedural antiplatelet drug is often used to reduce thrombotic complications. Therefore, further exploration of the interaction between the details of thrombectomy procedures and the safety and effectiveness of periprocedural antiplatelet drug is urgent. In the present study, we found that tirofiban did not increase the risk of sICH in patients with fewer than 3 passes, which implied that the use of perioperative antithrombotic therapy is feasible in selected patients. A secondary analysis of the RESCUE BT trial showed that intravenous tirofiban was associated with substantial reperfusion rates and favorable functional outcomes among patients with large artery atherosclerosis strokes.[22] Moreover, the recently published results from the ANGEL-REBOOT trial,[23] in which 96% of patients were treated with tirofiban, showed a lower incidence of sICH compared to our study (2.6% vs 7.3%). These findings indeed suggest that tirofiban may be safe in patients who have failed ICAS or thrombectomy. While there are differences in patient populations and study designs between our study and ANGEL-REBOOT, the results further validate the potential role of tirofiban in specific patient subgroups. Additionally, in the subgroup analyses of the MR CLEAN-MED (Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment) trial,[24] the point estimate of the therapeutic effect of unfractionated heparin on functional outcome was beneficial for patients with an onset of recanalization time of less than 195 min. Therefore, targeting the nature of the lesion, shorter procedure time and accurate application of perioperative antithrombotic therapy may be the future direction of EVT.

Interestingly, in the present study, we did not find a correlation between the number of passes and the development of sICH in the placebo group, which conflicts with the results reported by previous studies.[11,12,20] An important reason was the different periods for enrolled patients in these studies. A longitudinal study in the MR CLEAN Registry showed that compared to the early period, the functional outcome of EVT in the recent period was significantly improved.[25] Therefore, we believe that the relationship between the number of passes and sICH can be weakened through improvements in technology and materials for EVT but may be enhanced by preoperative use of tirofiban.

Notably, we found a correlation between prior antiplatelet history and the development of sICH in EVT patients, which was in line with a previous study.[26] Kim et al also showed that patients with prior antiplatelet history have a higher rate of early neurological deterioration-symptomatic hemorrhagic transformation (17%).[26] However, the mechanism is not clear. We considered that early administration of antiplatelet drugs in unselected patients treated with EVT does not improve outcomes by 3 months and may increase the risk of sICH. For example, the MR CLEAN-MED trial[24] was stopped early because periprocedural intravenous aspirin was associated with an increased risk of sICH without

improving functional outcome. Our findings also supported that early intravenous tirofiban administration before EVT may increase the risk of sICH. However, the Chemical Optimization of Cerebral Embolectomy (CHOICE) trial[27] showed that the use of adjunct intra-arterial alteplase after successful EVT could result in a greater likelihood of excellent neurological outcome at 90 days and not increase sICH compared with placebo. Therefore, the optimal antiplatelet timing during EVT also needs to be further validated in future studies. Additionally, several patient characteristics, such as multiple attempts and prior antiplatelet history, need to be considered before the administration of antiplatelet drugs. Our findings have the potential to provide an important reference for the clinical practice and future research design.

There are some limitations in our study. First, our conclusions were based on the dose regime used in the RESCUE BT trial. In fact, the efficacy and safety of other doses of tirofiban are still unclear and merited further evaluation in future studies. Second, since the reasons for multiple retrieval attempts are heterogeneous, we could not differentiate the underlying cause for multiple retrieval attempts, especially in patients with intracranial atherosclerosis. Third, the overall number of complications was low, and the statistical power was limited. In the present study, the risk of sICH was not significantly increased in patients with more than 3 passes. A main reason was that only 9.1% (79/866) of patients had more than 3 passes. Therefore, the results might be further assessed in larger patient cohorts. However, to our knowledge, this is the first large-sample study specifically assessing the interaction between the number of thrombectomy procedures and the safety and effectiveness of tirofiban in patients with EVT. Our results further supplemented the observation of the safety of using tirofiban in clinical practice. The strengths of our study were that good-quality randomized control trial data were analyzed, which increases the generalizability of the findings. Moreover, we included the most important confounders that may affect sICH. Additionally, all our imaging was assessed by an independent core laboratory.

Conclusion

In patients with multiple attempts, intravenous tirofiban may increase the risk of sICH. Further research and individualized risk assessment are necessary to determine the most appropriate strategy of intravenous tirofiban for EVT patients, especially considering details of thrombectomy procedures.

Abbreviations

EVT, endovascular therapy; sICH, symptomatic intracranial hemorrhage; FPE, first pass effect; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; MCA, middle cerebral artery; eTICI, Expanded Thrombolysis in Cerebral Infarction; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; CE, cardioembolism; LAA, large artery atherosclerosis.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki. The study was approved by the ethics committee of Xinqiao Hospital, Army Medical University, Chongqing, China, and each subcenter. Due to the study's anonymized, retrospective nature, the need for patient consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest.

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