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Safety and efficacy of tirofiban in acute ischemic stroke patients not receiving endovascular treatment: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The purpose of this systematic review and meta-analysis was to analyze the safety and efficacy of tirofiban when used for acute ischemic stroke (AIS) patients not undergoing endovascular treatment.

MATERIALS AND METHODS: An electronic search was performed for English-language studies on PubMed, Scopus, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) databases up to 31st July 2019. All types of studies comparing tirofiban monotherapy or combined intravenous (IV) thrombolysis and tirofiban therapy with controls for AIS patients were included. RESULTS: Six studies were included in the review. Three evaluated tirofiban monotherapy while three compared IV thrombolysis and tirofiban therapy with controls. Meta-analysis indicates that tirofiban monotherapy does not significantly increase the incidence of intracerebral hemorrhage (ICH) (Odds Ration [OR] 1.14, 95% CI 0.72-1.82, p = 0.57; I2 = 0%), symptomatic intracerebral hemorrhage (sICH) (OR 0.52, 95% CI 0.09-3.03, p = 0.46; I2 = 0%) and mortality (OR 0.53, 95% CI 0.13-2.07, p = 0.36; I2 = 63%) in AIS patients. Similarly, our analysis indicates no significant increase in the rates of ICH (OR 0.82, 95% CI 0.33-2.07, p = 0.68; I2 = 0%), sICH (OR 0.91, 95% CI 0.16-5.16, p = 0.91; I2 = 0%) and mortality (OR 1.50, 95% CI 0.42-5.38, p= 0.54; I2 = 0%) in AIS patients treated with combined IV thrombolysis and tirofiban therapy. Meta-analysis for functional outcome was not possible.

CONCLUSIONS: To conclude, tirofiban appears to be safe when used following IV thrombolysis or as monotherapy in AIS patients. Conclusions regarding improvement in functional improvement cannot be drawn. Further trials are needed to strengthen the evidence on this topic.

Key Words:
Tirofiban, Anti-platelet, Complications, Stroke, Thrombolysis.

Introduction

Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is an effective treatment option for patients with acute ischemic stroke (AIS)[1]. However, the narrow treatment window, initially limited to <3 h of symptoms onset, restricts this treatment option to less than 2% of stroke patients[2]. Treatment time has been extended up to 4.5 h after studies demonstrated that rt-PA in the 3 to 4.5-h window also results in a 7.2% absolute improvement as compared to placebo[3]. Regardless, bleeding complications, serious side effects, and lack of efficacy are still associated with rt-PA administered beyond the treatment time[4].

For patients receiving IV thrombolysis, the recanalization rate is estimated to be 46%[5]. However, reocclusion is a major limitation affecting around 14-34% of patients[6]. Reocclusion after initial recanalization has been attributed to the activation of platelet aggregation[7]. It is postulated that after recanalization, there is an accumulation of fibrinogen and platelets in the microcirculation leading to cerebral micro-thrombosis. Activated glycoprotein (gp) IIb/IIIa platelet receptors bind with fibrinogen molecules forming bridges between adjacent platelets thereby facilitating platelet aggregation and accumulation[8]. To counteract this effect, a group of highly selective platelet antagonists, the gp IIb/IIIa inhibitors have been advocated for acute stroke therapy[9]. These drugs reversibly block the fibrin binding receptors thereby preventing platelet aggregation. Evidence from animal studies[10] indicates that gp IIb/IIIa inhibitors are effective in reducing cerebral infarct volume, probably by the prevention of microvas-

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cular thrombosis and improving post-ischemic blood flow.

Tirofiban, a highly selective nonpeptide gp IIb/IIIa antagonist, is approved by the Food and Drug Administration for the treatment of acute coronary syndrome[11]. Following its success in the management of ischemic heart disease, the drug has been investigated for improving outcomes in AIS patients[12]. It has a short half-life of 2 h and prolonged bleeding due to the drug is rapidly restored within 3 h of stoppage. The occurrence rate of drug-induced thrombocytopenia is also low at 0.5-2%[9]. Several clinical trials have evaluated the role of tirofiban in acute stroke therapy. While Junghans et al[9] indicate tirofiban may be safe in patients with AIS undergoing endovascular treatment, literature is devoid of level 1 evidence for tirofiban used singly or following IV thrombolysis in AIS patients. Therefore, the purpose of this investigation was to systematically search the literature and analyze evidence on the safety and efficacy of tirofiban when used for AIS patients not undergoing endovascular treatment.

Materials and Methods

Search Strategy

We searched for English-language studies on PubMed, Scopus, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) databases up to 31st July 2019. Search terms used were: "tirofiban"; "anti-platelet"; "glycoprotein IIb-IIIa inhibitors"; "thrombolysis" and "stroke". Additionally, we performed a hand search of references of included published articles and pertinent review articles for the identification of any additional studies. Two reviewers independently performed the literature search. After evaluating the title and abstract level, full texts of selected articles were scanned for inclusion in the review. Any disagreements were resolved by discussion. Guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[13] and Cochrane Handbook for Systematic Reviews of Intervention[14] were followed during the conduct of this review.

Inclusion Criteria

Population, Intervention, Comparison, Outcome, and Study design (PICOS) outline was used for identifying studies for inclusion. We included all types of studies conducted on acute ischemic stroke patients not receiving any endovascular treatment (*Population*) but treated with either tirofiban monotherapy or combined intravenous (IV) thrombolysis and tirofiban therapy (*Intervention*). Studies were to have a control group (*Comparison*) and should have evaluated the safety and efficacy of tirofiban (*Outcomes*). Safety was defined as the incidence of intracerebral hemorrhage (ICH), symptomatic intracerebral hemorrhage (sICH), and mortality. Efficacy of tirofiban was measured in terms of functional improvement assessed on the National Institute of Health Stroke Scale (NIHSS) or modified Ranking Scale (mRS). We excluded studies conducted on stroke patients undergoing endovascular treatment and single-arm trials. Animal studies, studies with duplicate data set, case-series, and case reports were also excluded.

Data Extraction and Outcomes

Data were extracted from the included trials by two independent reviewers. The following details were sourced: authors, publication year, study design, sample size, baseline patient characteristics, tirofiban protocol, IV thrombolysis protocol, and study outcomes. Primary outcomes were the incidence of any ICH, sICH, and mortality. The secondary outcome was functional improvement measured on the NIHSS or mRS.

Risk of Bias

Studies other than Randomized Controlled Trials (RCTs) were evaluated using the risk of bias assessment tool for non-randomized studies (RoBANS)[15]. Studies were rated as low risk, high risk, or unclear risk of bias for selection of participants, confounding variables, intervention measurements, blinding of outcome assessment, incomplete outcome data, selective outcome reporting. RCTs were assessed using the Cochrane Collaboration risk assessment tool for RCTs[16]. Studies were rated as low risk, high risk, or unclear risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Statistical Analysis

Outcomes were summarized using the Mantel-Haenszel Odds Ratios (OR) with a 95% confidence interval (CI). Anticipating methodological heterogeneity, we used a random-effects model to calculate the pooled effect size. Heterogeneity was calculated using the I^2 statistic. I^2 values of 25-50%

represented low heterogeneity, values of 50-75% medium heterogeneity and >75% represented substantial heterogeneity. We also performed a sensitivity analysis to evaluate the influence of each study on the overall result. Using the one-study-out method, we evaluated whether eliminating each study would significantly change the pooled effect size. Review Manager (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis.

Results

A total of 192 records were identified after the removal of duplicates (Figure 1). Full texts of eight articles were scanned and two of them were excluded. Seitz et al[17] reported a duplicate data set whereas Lin et al[18] included patients with AIS with no evidence of arterial occlusion and no area of hypoperfusion on imaging studies. Since this selection criterion was not used in any of the other studies, to maintain homogeneity this study was excluded. Six studies[9,19-23] met the inclusion criteria and were included in the review.

We divided the studies into two groups. The first group included studies utilizing tirofiban monotherapy while the second group consisted of studies employing combined IV thrombolysis and tirofiban therapy.

Characteristics of Included Studies

Three studies[9,20,21] compared tirofiban monotherapy with control (Table I). Two were RCTs[20,21]

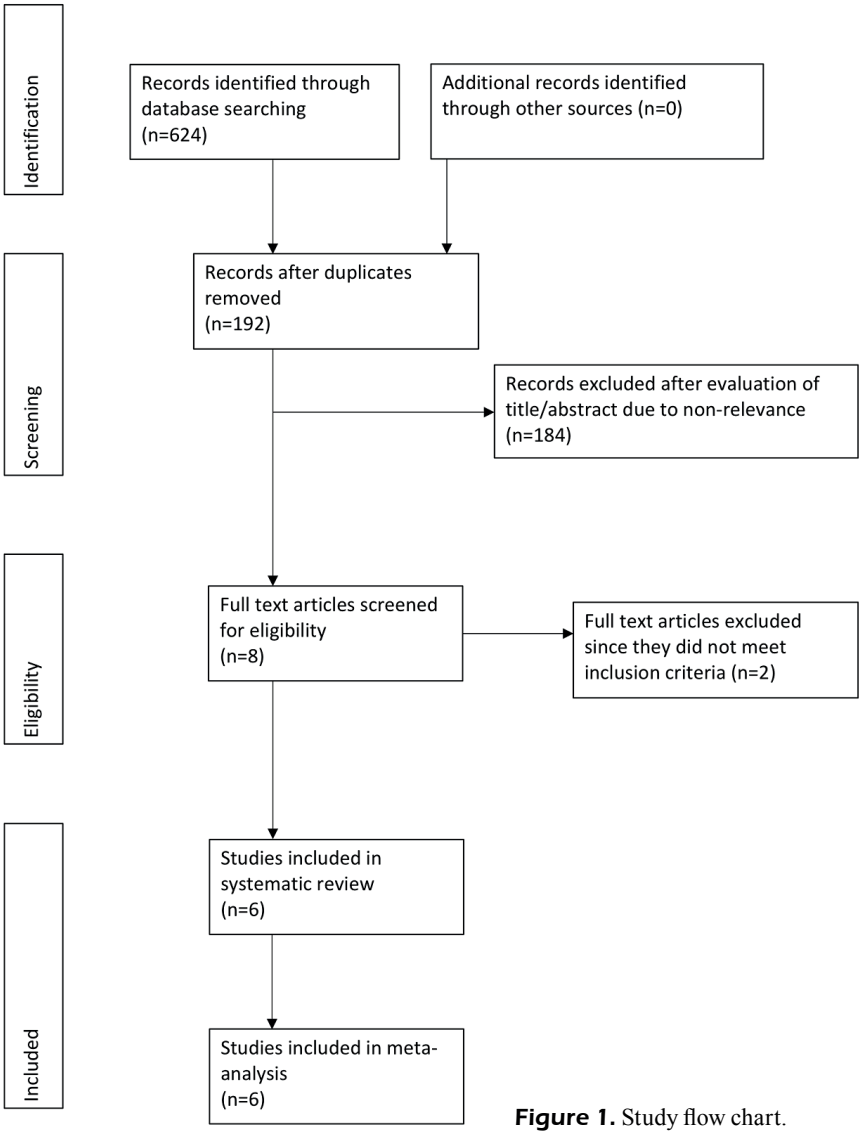

Figure 1. Study flow chart.

Table I. Characteristics of included studies with tirofiban monotherapy.

Author/Year	Study Type	Sample size		Tirofiban dose	Other medications	Onset to treatment time (Mean ± SD)	NIHSS score mean (range)	
		Tirofiban group	Control group				Tirofiban group	Control group
Junghans et al[9]/2001	Retrospective	18	17	0.4 μg/kg body weight/min for 30 min followed by a continuous infusion of 0.1 μg/kg body weight/min for at least 24 h	For both groups, UFH targeted to an aPTT of 50-70 s	10±13 h	ESS: 83 (32-94)	ESS: 72 (30-98)
Torgano et al[20]/2010	RCT	75	75	0.6 μg/kg/min for 30 min followed by 0.15 μg/kg/min for 72 h or less in case of adverse reactions or reduction in the NIHSS score to 0-1	CG: Aspirin 300mg-daily for 3 days	4.4±1.04 h	9 (6-16)	9 (7-14)
Seibler et al[21]/2011	RCT	131	129	0.4 μg/kg body weight/min for 30 min followed by a continuous infusion of 0.1 μg/kg body weight/min for 48 h	Additional antiplatelet drugs allowed	SG: 2.8 h CG: 3.2 h	6 (4-18)	6 (4-18)

RCT, Randomized controlled trial; UFH, Unfractionated heparin; aPTT, activated partial thromboplastin time; s, seconds; ESS, European Stroke Scale; NIHSS, National Institute of Health Stroke Scale; kg, Kilogram; min, minute; h, hour; CG, control group; SD, Standard Deviation.

while one was a retrospective study[9]. The control group received aspirin in one trial[20], while Junghans et al[9] used unfractionated heparin targeted to an aPTT of 50-70s for both groups. The dose of tirofiban was more or less similar across the three studies; however, the duration of infusion varied.

For combined IV thrombolysis and tirofiban therapy, three studies[19,22,23] were identified and included (Table II). There were two retrospective studies[19,22], while one was an RCT[23]. In the three studies, 135 patients were treated with IV thrombolysis followed by tirofiban therapy while 223 patients receiving IV thrombolysis served as controls, and tirofiban dosage was similar. In Seitz et al[19], Heparin was administered in both study and control groups in one study. Symptom onset to treatment time was less than 3 h in two studies[19,22] and less than 4.5 h in one trial[23]. Liu et al[23] reported the efficacy of tirofiban administered at different time points within 24 h of IV thrombolysis. To match with the remaining studies, we included data of tirofiban administered within 2 h of thrombolysis.

Primary Outcomes

Tirofiban Monotherapy

The incidence of ICH was 23.47% (50/213) with tirofiban monotherapy and 21.29% (46/216) in control group. The difference was not statistically significant (OR 1.14, 95% CI 0.72-1.82, p = 0.57; I^2 = 0%) (Figure 2A). The overall incidence of sICH was low; with 2/213 patients (0.9%) in the study group and 4/216 patients (1.8%) in the control group developing this complication. Our meta-analysis did not find any significant difference between the two groups (OR 0.52, 95% CI 0.09-3.03, p = 0.46; I^2 = 0%) (Figure 2B). 4.93% (11/223) patients died in tirofiban group while 8.71% (19/218) died in control group. Our results indicate that tirofiban monotherapy is not associated with an increased risk of mortality (OR 0.53, 95% CI 0.13-2.07, p = 0.36; I^2 = 63%) (Figure 2C).

IV Thrombolysis with Tirofiban Therapy

5.92% (8/135) patients developed ICH following IV thrombolysis and tirofiban therapy, while

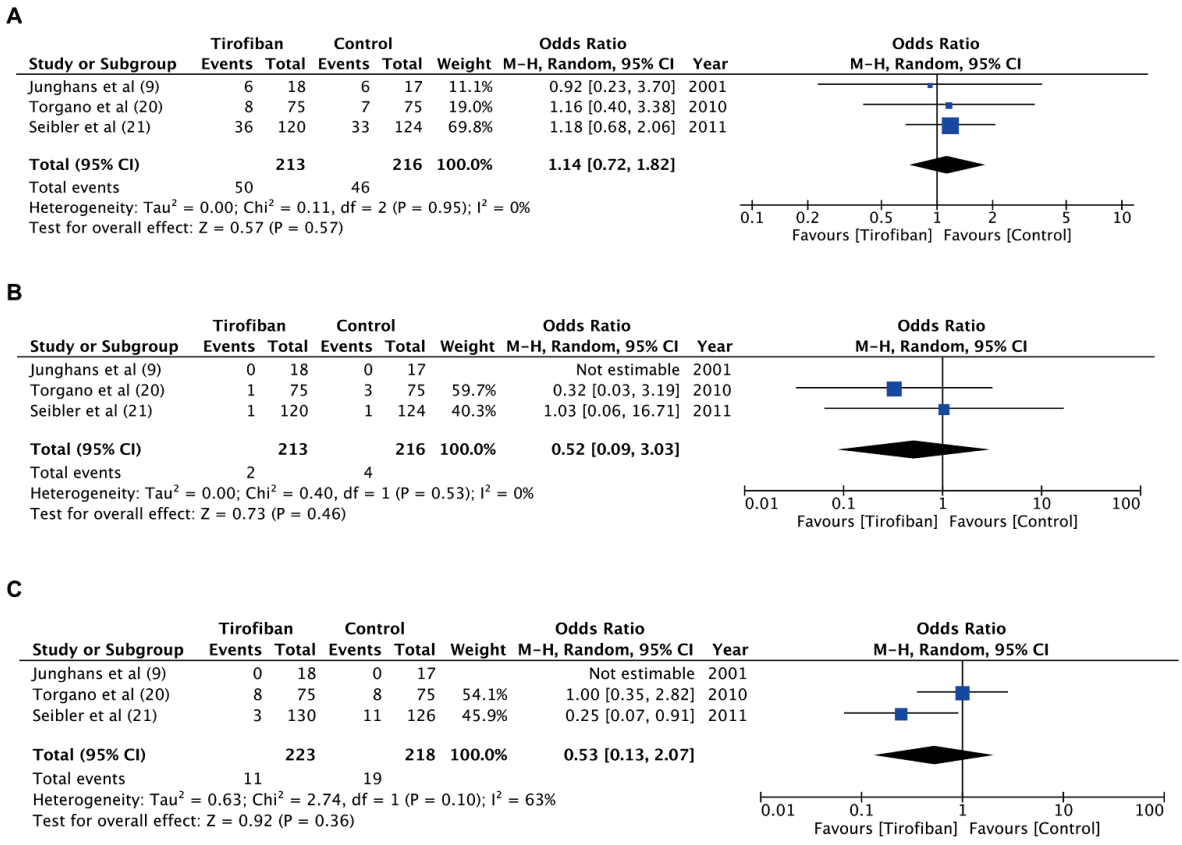

Figure 2. Forrest plot of tirofiban monotherapy *vs.* control for **(A)** any intra-cerebral hemorrhage (ICH). **B,** Symptomatic intra-cerebral hemorrhage (sICH). **C,** Mortality.

Table II. Characteristics of included studies with intravenous thrombolysis and tirofiban therapy.

Author/ Year	Study Type	Sample size		Tirofiban dose	IV thrombolysis protocol	Common medications	Onset to tirofiban infusion time	NIHSS score mean (range) or mean±SD	
		Tirofiban group	Control group					Tirofiban group	Control group
Seitz et al[19]/2003	Retrospective	37	119	0.4 μg/kg body weight/min for 30 min followed by a continuous infusion of 0.1 μg/kg body weight/min for at least 24 h	SG: rtPA bolus 24±9mg CG: rtPA 0.9 mg/kg body weight over 1 h with a 10% bolus	SG: continuous infusion of 10000 IU of UFH with tirofiban CG: Low-dose heparin and aspirin after 24 h	Less than 3 h	NR	NR
Li et al[22]/2016	Retrospective	41	41	0.4μg/kg body weight/min for 30 min followed by a continuous infusion of 0.1 μg/kg body weight/min for at least 24 h	Alteplase 0.9 mg/kg body weight	None	Less than 3 h	8 (4-18)	10 (4-18)
Liu et al[23]/2019	RCT	57	63	0.5μg/kg body weight/min for 30 min followed by a continuous infusion of 0.1 μg/kg body weight/min for at least 24 h	Alteplase 0.9 mg/kg body weight	None	Less than 4.5 h	10.11±5.04	10.38±4.68

RCT, Randomized controlled trial; UFH, Unfractionated heparin; NIHSS, National Institute of Health Stroke Scale; kg, Kilogram; min, minute; h, hour; SG; Study group; CG, control group; NR, Not Reported; IV, Intravenous; rtPA, recombinant tissue plasminogen activator; SD, Standard Deviation; IU, International Units.

the same was reported in 7.17% (16/223) with IV thrombolysis alone. Pooled analysis indicated no significant difference (OR 0.82, 95% CI 0.33-2.07, $p = 0.68$; $I^2 = 0\%$) (Figure 3A). sICH was reported in 2/135 patients (1.48%) receiving tirofiban and in 5/223 patients (2.24%) not receiving the drug. The difference was statistically not significant (OR 0.91, 95% CI 0.16-5.16, $p = 0.91$; $I^2 = 0\%$) (Figure 3B). With an overall mortality of 2.96% (4/135) with tirofiban and 3.13% (7/223) in the control group, meta-analysis indicated no statistically significant difference (OR 1.50, 95% CI 0.42-5.38, $p = 0.54$; $I^2 = 0\%$) (Figure 3A).

Sensitivity analysis was carried out for all primary outcomes of both groups of studies. No change in results was noted for any variable.

Secondary Outcomes

In the absence of a common definition of "improved functional outcome" and difference in the scoring methods, a meta-analysis was not conducted for functional outcomes. Instead, the results of the included studies are presented in a descriptive form.

Tirofiban Monotherapy

Of the three studies analyzing tirofiban monotherapy, Junghans et al[9] reported functional outcomes measured on the European Stroke Scale (ESS). They reported that the proportions of patients with recovery (65 *vs.* 67%), stable deficit (29 *vs.* 28%) or slight deterioration (6% *vs.* 5%) were almost identical in both the tirofiban group and control group. Torgano et al[20] defined favorable outcomes as NIHSS reduction of ≥4 points at 72 h and mRS scores of 0-1 at 3 months. NIHSS reduction of ≥4 points was seen in 56% of patients in both groups. 45% of patients in the tirofiban group and 53% of patients in the control group achieved a favorable outcome at 3 months. The was no statistically significant difference between the two groups. Siebler et al[21] explored functional outcomes on the mRS and Barthel Index at 5 months and reported no difference between the two groups.

IV Thrombolysis with Tirofiban Therapy

Seitz et al[19], in a matched comparison of 23 patients in the study group and 20 patients in the

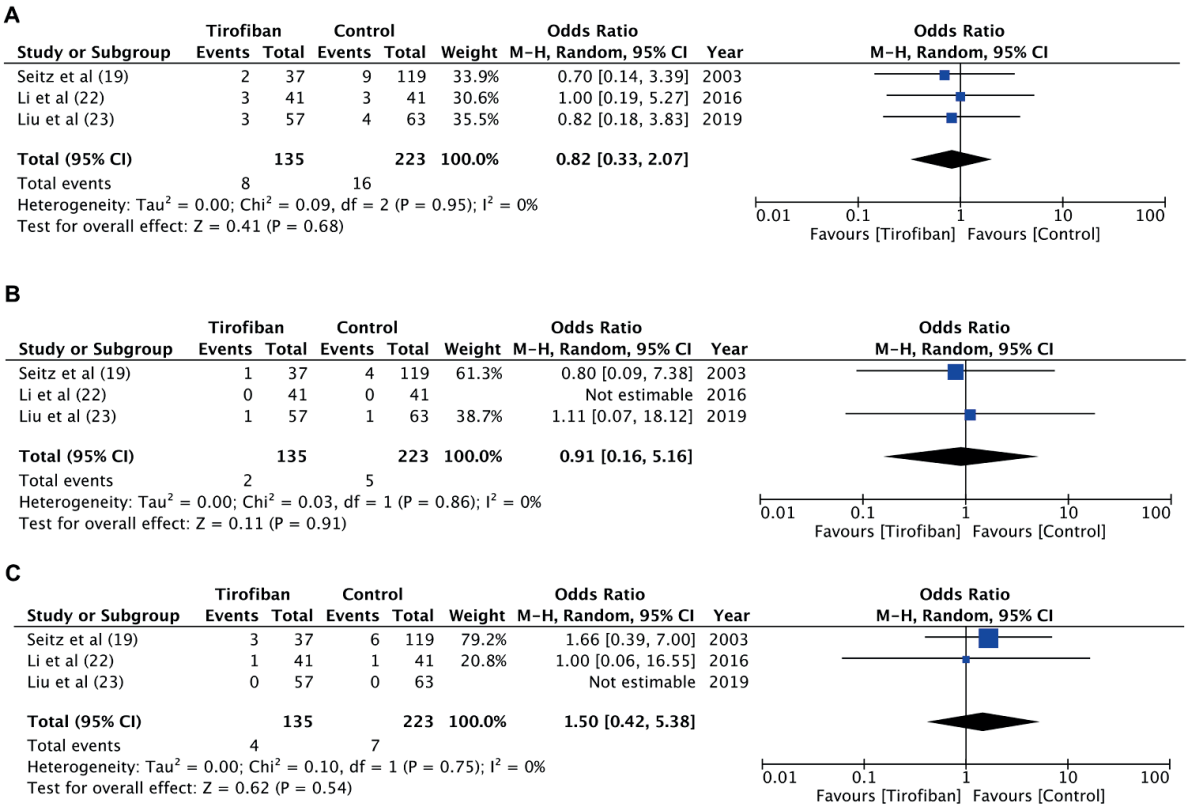

Figure 3. Forrest plot of IV thrombolysis with tirofiban therapy vs. IV thrombolysis only for **(A)** any intra-cerebral hemorrhage (ICH). **B,** Symptomatic intra-cerebral hemorrhage (sICH). **C,** Mortality.

Table III. Authors judgement of risk of bias in included studies.

RCTs							
Study	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Other Biases**
Torgano et al[20]	Unclear risk	Unclear risk	Low risk	High risk	Low risk	Unclear risk	Low risk
Seibler et al[21]	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Liu et al[23]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Low risk
Non-RCTs							
Study	**Selection of participants**	**Confounding variables**	**Intervention measurements**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective outcome reporting**	
Junghans et al[9]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	
Seitz et al[19]	High risk	Low risk	Low risk	High risk	Low risk	High risk	
Li et al[22]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	

RCT, Randomized control trial.

control group, reported outcomes on the Ranking Scale. On discharge, 63% and 55% of patients in the study and control groups respectively, reached a score of 0-2. Li et al[22] reported that NIHSS score at 7 days was significantly lower with alteplase/tirofiban as compared to alteplase alone (1 *vs.* 6, $p = 0.002$). Also, a favorable outcome, defined as mRS score of 0-1 at 3 months was better in the study group than in the control group ($p = 0.026$). Liu et al[23] defined good functional outcomes as mRS score of 0-2 at 3 months. 78.9% of patients achieved good functional outcome with tirofiban as compared to 61.9% in control group. The difference was statistically significant ($p<0.05$).

Risk of Bias Summary

The authors' judgment of the risk of bias summary is presented in Table III. Amongst RCTs, randomization was clearly described in one trial[21], blinding of participants[20], and outcome assessment[21] was mentioned in one trial each. Only one trial was pre-registered[21]. For non-RCTs, Junghans et al[9] and Li et al[22] reported the inclusion of both study and control samples from the same unit. All three studies[9,19,22] considered matching the study groups on baseline variables. Only reported the blinding of outcome assessment. All outcomes were clearly reported only in Li et al[22].

Discussion

Gp IIb/IIIa inhibitors, a group of anti-platelet drugs, have been widely used in high-risk myocardial infarction (MI) patients undergoing IV thrombolysis or percutaneous coronary intervention to prevent platelet aggregation and thrombus formation[8]. However, despite the success seen in cardiovascular medicine, early use of gp IIb/IIIa inhibitors in stroke was limited by the possibility of hemorrhagic transformation and the heterogeneous pathogenesis of the disease[24]. The 2018 American Heart Association/American Stroke Association (AHA/ASA) guidelines do not recommend concurrent administration of anti-platelet drugs with IV thrombolysis[25]. These recommendations are based on the results of anti-platelet drugs like aspirin, eptifibatide, and abciximab and absence of strong evidence demonstrating improved outcomes with early administration of anti-platelets. The role of aspirin after IV thrombolysis was explored by the Anti-platelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke (ARTIS) trial[26]. The study was stopped prematurely due to the high incidence of sICH with aspirin with no concomitant clinical improvement. Eptifibatide was investigated in the CLEAR trial, which found the drug to be safe but demonstrated no significant beneficial effect of combining eptifibatide with IV thrombolysis[27]. Of particular interest are the negative effects seen with abciximab in the AbESTT-II trial[28]. This RCT enrolled stroke patients and randomized them to receive abciximab within 6 h of stroke onset. Functional improvement was seen in 32% in study group and 33% in placebo group, with no significant difference. However, the trial was halted due to a 6-fold increase in sICH in study group.

The high incidence of sICH with aspirin could be attributed to its irreversible and nonselective inhibitory effect on platelet aggregation[26]. Similarly, higher bleeding complications with abciximab could be due to the drugs' irreversible inhibition of platelet gp IIb/IIIa receptors and its long half-life of 8 h[28]. In contrast, tirofiban binds reversibly with gp IIb/IIIa receptors and has a short half-life of 2 h. This may explain the lower risk of hemorrhagic complication seen with tirofiban[12]. The lower risk of bleeding with tirofiban as compared to abciximab and eptifibatide has been demonstrated in MI patients[11]. While there have been no direct comparative studies between tirofiban and abciximab for AIS, the relative safety of tirofiban administered within 24 h of stroke has been demonstrated by several trials[19,21-23]. A recent meta-analysis[12] has evaluated the safety of tirofiban in AIS patients undergoing endovascular treatment. Their results indicate that tirofiban does not increase the risk of any ICH, sICH, and mortality when administered immediately after the endovascular treatment of AIS.

The specific aim of our review and meta-analysis was to evaluate the safety of tirofiban administered early, either as monotherapy or following IV thrombolysis. Given the limited number of studies available in literature and the small sample size of the included studies, the total number of participants in the study and control group was not high. However, the results of our review concur with the results of the previous meta-analysis[12] analyzing the safety of tirofiban following endovascular treatment. Our pooled analysis indicates that tirofiban does not seem to increase the risk of any ICH, sICH or mortality when administered as monotherapy or following IV thrombolysis. Also, none of the included studies individually reported any significantly increased risk of ICH and mortality with tirofiban.

One of the primary aims of exploring the addition of tirofiban to AIS treatment is to improve functional outcomes. While animal models suggest that tirofiban may improve functional outcomes with early administration[29], clinical studies do not completely corroborate with these findings. Guo et al[12] in their meta-analysis found no association between tirofiban therapy and functional outcome or recanalization rates when the drug was administered following endovascular treatment. As a secondary objective, our study also attempted to evaluate the efficacy of tirofiban in improving clinical outcomes. However, heterogeneity of definitions and limited data precluded a meta-analysis for this variable. Descriptive analysis indicated that none of the studies evaluating tirofiban monotherapy reported significant improvement in functional outcomes with the drug. However, studies on combined IV thrombolysis and tirofiban reported significantly better outcomes with rt-PA + tirofiban as compared to rt-PA alone. It is postulated that post IV thrombolysis, once the action of rt-PA wears off, the increased thrombotic activity can be blocked by tirofiban. Therefore, the thrombolytic effects of rt-PA are maintained for a longer period with possible improvement in functional outcomes[17,19]. Since one of the primary potential actions of tirofiban is to prevent arterial reocclusion following IV thrombolysis[21], it is important to evaluate any difference in recanalization rates with or without the drug. Recanalization rates were reported by only one[23] of the three trials comparing combined IV thrombolysis and tirofiban with control. The authors reported no difference in the recanalization rate between rt-PA + tirofiban and rt-PA alone, possibly due to the small sample size of the study. Due to limited evidence and paucity of high-quality studies, conclusions on the efficacy of tirofiban for AIS patients not receiving endovascular treatment cannot be drawn at this point. There is a need for further trials to explore the beneficial effect of the drug for AIS patients.

Some limitations need to be highlighted. First, only three studies were available for inclusion in each group of this review. Due to the limited data and small sample size of the included studies, conclusions could not be drawn. Second, the quality of the included studies was not high. Three of the six included studies were non-RCTs. The inherent risk of bias associated with observational studies could have influenced our results. Third, there was heterogeneity amongst the included studies concerning the use of other anti-coagulants and anti-platelet drugs. Tirofiban was administered singularly in only two[22,23] of the six included studies. In the remaining four studies, different anti-coagulants or anti-platelet drugs were used. Due to a limited number of studies, this review was unable to discern a difference in outcomes with singular use of tirofiban or when used in combination with other anticoagulant and antiplatelet drugs.

Conclusions

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the safety and efficacy of tirofiban for AIS patients not receiving endovascular treatment. Our results indicate that tirofiban may be safe when administered early as monotherapy or following IV thrombolysis in AIS patients. The role of the drug in improving functional outcomes is not clear. Further studies with large sample size and homogenous methodology are required to provide robust evidence.

Conflict of Interests

The Authors declare that they have no conflict of interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JZ conceived and designed the study. JZ, YG, and QM collected the data and performed the literature search. JZ was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

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