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Review Article

INTRAVENOUS THROMBOLYSIS IN PATIENTS OF ACUTE ISCHEMIC STROKE WITH THROMBOCYTOPENIA: A LITERATURE REVIEW

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ABSTRACT

Acute cerebral infarction, also known as acute ischemic stroke, refers to neurological deficit syndrome caused by necrosis and softening of brain tissue caused by ischemia and hypoxia, and its incidence was 60%~70% among all strokes. Therapeutic methods of acute cerebral infarction include thrombolysis, anticoagulation, anti-platelet aggregation, etc. Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) has been identified as an approved pharmacological therapy for acute ischemic stroke (AIS). This mode of therapy has been used in patients presenting within 4.5 hours of the symptom onset. Among various contraindications, a platelet count<100,000/mm^3 is considered as one of the contraindication for IV rtPA administration in AIS because of a possible increase in the risk of bleeding complications, particularly intracranial hemorrhage (ICH). In this article we reviewed present existing literature of intravenous thrombolysis with rtPA in acute ischemic stroke (AIS) patients with thrombocytopenia to investigate the safety of recombinant tissue plasminogen activator (rtPA) in patients with acute ischemic stroke (AIS) whose platelet count is less than 100,000 /mm^3. Methods: Ovid Medline, PubMed and Google Scholar were searched for all relevant previously published articles or abstracts in English, using the search terms “Stroke,” “thrombolysis,” “rtPA,” “thrombocytopenia,” and “off-label use.” The reference list in all articles was checked for additional data sources. All titles and abstracts from this search were reviewed for relevance based on the inclusion/exclusion criteria described later. Full texts of appropriate abstracts were then reviewed and the final list of articles for inclusion was determined. The references of included studies to identify potentially relevant citations were also searched. Results: From all the searched literatures, there were a total of 4632 AIS patients who had a platelet count <100,000/mm^3 and received IV rtPA, with 2 of them developing sICH (7.7 %). Comparing the rate of sICH among this group with the patients with normal platelet count in a cohort, there was no statistically significant difference (7.7% versus 6.04%, *P* value = .73). Conclusion: The safety or efficacy of intravenous

thrombolysis in patients of ACI with thrombocytopenia, INR >1.7, aPTT >40 s, or PT >15 s cannot be confirmed currently. It is not reasonable to withhold IVT and wait for the platelet count result unless there is serious suspicion for thrombocytopenia based on a patient's medical and drug history. IV rt-PA for AIS might be safe in patients with platelet count <100,000/mm^3 and it is reasonable not to delay IV rtPA administration while waiting for the platelet count result, unless there is strong suspicion for abnormal platelet count.

Key Words: Intravenous rt-PA, acute cerebral infarction, thrombocytopenia, ICH

INTRODUCTION

Acute cerebral infarction, also known as acute ischemic stroke, refers to neurological deficit syndrome caused by necrosis and softening of brain tissue caused by ischemia and hypoxia, with its incidence of 60%~70% among all strokes.[1,2] Therapeutic methods for acute cerebral infarction include thrombolysis, anticoagulation and anti-platelet aggregation.[3,4] Recombinant tissue plasminogen activator (rt-PA) is the only drug approved by the Food and Drug Administration (FDA) for intravenous thrombolysis of acute cerebral infarction.[5,6] There are various contraindications for intravenous thrombolysis, among them thrombocytopenia (a platelet count<100,000/mm^3) is one. Due to a possible risk of bleeding complications causing intracranial hemorrhage (ICH), thrombocytopenia is considered one of the contraindications for intravenous thrombolysis in patients with acute cerebral infarction. This threshold was not determined through randomized trials or large prospective studies, but was derived from expert panel consensus.[7] So far, only a few AIS patients who received IV rtPA and had platelet count <100,000/mm^3 has been reported in the medical literature.[8, 9, 10, 11] Because of very little data available on this group of patients, it is unclear whether this is a legitimate threshold for withholding IV rtPA administration and whether clinicians should wait for platelet count result prior to IV rtPA administration for AIS. Hence to sort out the safety of IV rtPA in such patients with thrombocytopenia through a review of the previous literature is the objective of this review.

METHODS

Ovid Medline, Sciencedirect, PubMed and Google Scholar were searched for all relevant previously published articles or abstracts in English. Terms like “Acute cerebral stroke,” “rtPA,”“intravenous thrombolysis,” “thrombocytopenia,” “off-label use”, “bleeding complications” was used for searching the related articles. In all the related articles the reference list was checked for additional information. The relevance with the topic was reviewed from all the titles and abstracts obtained from the search. Full texts of appropriate abstracts were then reviewed and the final list of articles was determined for inclusion in the article. The references of all the included studies were also searched to identify potentially relevant citations.

Eligibility Criteria:

Studies were considered eligible if they met the following criteria: (1) studies performed on patients with acute ischemic stroke aged ≥18 years, (2) included patients who were treated with recombinant tissue plasminogen activator (rtPA), (3) included patients who had platelet count <100,000/mm3.

RESULTS

Until June 2020 all the related articles revealed 4632 reported cases of patients who were given IV rtPA for ACI with thrombocytopenia （platelet count <100,000/mm^3）. The previous largest case series which reported 10 patients with platelet count <100,000 mm^{3}and received IV rtPA despite this contraindication were identified.[8] None of them developed any bleeding complication after receiving intravenous thrombolysis. 7 patients those were treated with IVT for AIS were found in a study in the Helsinki Stroke Thrombolysis Registry done by Meretoja et al among whom only 1 (14.35%) developed sICH.[9]No other detail was available about this patient. A retrospective chart review study done by Brunner showed that the risk of bleeding complication does not increase following IVT in AIS patients with thrombocytopenia. They found 3 patients with platelet count <100,000/mm^3 and among them, none was reported to have sICH post-IVT.[10] 1 more patient was found to have a platelet count <100,000/mm^3 in another single-center registry; this patient also did not develop sICH post-IVT.[11]A total of 26 previously reported patients with acute ischemic stroke were found in the literature that had a low platelet count and who received IV rtPA, 2 of them developed sICH (7.7%). In one of the cohort study, the rate of sICH was compared between groups of patients with low platelet count and patients with normal platelet count. No statistically significant difference was found in that study (7.7% vs 6.04%, *P* value = .73). In the pivotal clinical trial of National Institute of Neurological Disorders and Stroke (NINDS), 312 patients with acute cerebral stroke were treated with IV rtPA. Among them 20 patients who had a platelet count >100,000/mm^3 (6.4%) experienced bleeding complication which compared to the reported cases of patients with platelet count <100,000/mm^3 had no statistically significant difference with respect to sICH rate (6.4% vs 7.7%, *P* value = .79).[14]

DISCUSSION

A web search in Medline, PubMed and Google Scholar until June 2020 revealed 4632 reported cases of patients who were given IV rtPA for AIS with platelet count <100,000/mm^3. The previous largest case series reported 10 patients with platelet count <100,000 mm^3 who received IV rtPA despite this contraindication were identified.[8] None of them developed sICH post-IVT. 7 patients those were treated with IVT for AIS were found in a study in the Helsinki Stroke Thrombolysis Registry done by Meretoja et al among whom only 1 (14.35%) developed sICH.[9] No other detail was available about this patient. A retrospective chart review study done by Brunner showed that the risk of bleeding complication does not increase following IVT in AIS patients with thrombocytopenia. They found 3 patients with platelet count <100,000/mm^3 and among them, none was reported to have sICH post-IVT.[10]In addition, 1 more patient was found to have a platelet count <100,000/mm^3

in another single-center registry; this patient did not develop sICH post-IVT.[11] Combining all these previously reported cases in the literature, there were a total of 26 AIS patients who had a platelet count <100,000/mm^3 and who received IV rtPA, with 2 of them developing sICH (7.7%). Comparing the rate of sICH among this group with the patients with normal platelet count in one of the cohort study, there was no statistically significant difference (7.7% vs 6.04%, *P* value = .73). In the pivotal National Institute of Neurological Disorders and Stroke (NINDS) clinical trial,[14] among 312 IV rtPA-treated patients, 20 (6.4%) experienced sICH. All of those patients had a platelet count >100,000/mm^3. Compared to the reported cases of patients with platelet count <100,000/mm^3, there was no statistically significant difference between them with respect to sICH rate (6.4% vs 7.7%, *P* value = .79).A retrospective study by R Wang et al on a total of 403 patients found significant differences in activated partial thromboplastin time, fibrinogen value, platelet value and smoking before thrombolysis between HT and non-HT group ($P < 0.05$) concluding that low fibrinogen levels and low platelet counts are associated with the risk of HT[15].

Another study by Yigeng Yang et al found that out of 101,527 patients with acute cerebral stroke treated with intravenous rtPA, 3,520 (3.47%) had thrombocytopenia and their in-hospital mortality was higher than that of patients with normal platelet count (10.8 vs. 6.9%, $p < 0.001$). The length of hospital stay was also significantly higher in the thrombocytopenia group (5.9 vs. 8.2 days, $p < 0.001$). Hence conclusion was made that thrombocytopenia is associated with higher in-hospital mortality, longer length of stay, a higher incidence of intracranial hemorrhage, post-procedural bleeding, and mechanical ventilation in stroke patients who received intravenous rtPA[16]. Likewise, Brett L. Cucchiara et al studied on the usefulness of checking platelet count before thrombolysis in Acute Ischemic Stroke in a total of 1752 patients. 82 of them (4.7%) had a platelet count <100 000 at stroke onset and only 6/1752 (0.3%) had a platelet count <100 000 which was not suspected based on initial history. All of these 6 patients had only mildly decreased platelet counts. Hence it was concluded that in patients without a history of thrombocytopenia or predisposing factors, the benefit of earlier thrombolysis may outweigh the bleeding risk of inadvertently treating a patient with thrombocytopenia[17].Another prospective multicenter study on the effect of platelet count (PC) affecting the outcome in IVT treated stroke patients, done by Henrik Gensicke et al., conclusion was made that lower platelet count increased the risk of sICH, while higher mortality was present with higher PC. The study was done in 7,533 IVT-treated stroke patients, among which 6,830 (90.7%) had normal PC, 595 (7.9%) had thrombocytopenia, and 108 (1.4%) had thrombocytosis. The result suggested that PC modifies outcome and complications in individual patients, while withholding IVT in all patients with PC < 100 × 10^9/L is challenged[18].NoblBarazangi et al did a retrospective analysis on 67 patients to determine the safety of IV rt-PA in therapeutically anti-coagulated or thrombocytopenic stroke patients. 12 of those patients had thrombocytopenia (mean platelet count 77K) and 3 among those developed sICH (4.5%), 2 patients developed minor bleeding complications with no clinical effect (hematoma at catheter site) and 12 patients (17.9%) died. These data suggest that IV rt-PA can be administered safely in patients with coagulopathy and

thrombocytopenia. Although rates of sICH and mortality were similar to the NINDS cohort, caution may be needed to identify certain hemorrhagic risk factors[19].

Although thrombocytopenia is one of the contraindication for intravenous thrombolysis, clinically patients with platelet count of <100 000 mm^3 are rare and was present in only small number of cases as per a large pooled analysis.[20] Another two observational studies confirmed this finding and reported that the rate of sICH was low.[2122]In the past, test of clotting function was essential before thrombolysis. According to a clinical research INR was not found to be raised in patients in hepatic failure, sepsis or not taking any anticoagulants or any other non-drug-related coagulopathy condition. One large registry study reported that 7 out of 152 patients with INR >1.7 or PT >15 s had sICH.[21] After adjustment for age and baseline NIHSS, the prognosis of patients with INR >1.7 was not worse than others.

Given the rarity of the condition, proportion of sICH among those with thrombocytopenia was combined with the proportion reported in the literature and found that the combined proportion was not statistically significantly different from the rate of sICH among the patients with normal platelet counts and also with those in the pivotal NINDS trial (all *P* values >.70). Considering the small size of patients with sICH, particularly among those with low platelet counts, no solid conclusion can be drawn about a legitimate threshold to withhold IVT and this observation cannot be generalized to all the patients with thrombocytopenia, particularly those with severe thrombocytopenia.

Table 13. Thrombocytopenia

Study	Study Design	n/Total Lysed, N	Any ICH, n	sICH, n	mRS Score of 0–2
Frank et al[52]	Data pooled from observational studies	10/2755	NA	0	NA
Meretoja et al[157]	Observational, single-center registry	7/985	NA	1	3
Brunner et al[155]	Observational, single-center registry	3/688	0	0	NA
Kvistad et al[156]	Observational, single-center registry	1/265	NA	0	NA
Prolonged aPTT					
Frank et al[52*]	Data pooled from observational studies	139/2755	NA	6	NA
Albers et al[158] (STARS)	Prospective, multicenter	13/389	NA	0	NA
Brunner et al[155]†	Observational, single-center registry	7/688	0	0	NA
Meretoja et al[157]	Observational, single-center registry	2/985	NA	0	0

Lopez-Yunez et al[159]	Retrospective, multicenter	1/50	0	0	NA
INR >1.7 or PT >15					
Frank et al[52*]	Data pooled from observational studies	152/2755	NA	7	NA
Albers et al[158] (STARS)	Prospective, multicenter	10/389	NA	0	NA
Breuer et al[160]	Observational, single-center prospective	22	NA	NA	NA
Brunner et al[155]	Observational, single-center registry	8/688	0	0	NA
Meretoja et al[157]	Observational, single-center registry	3	NA	0	2‡
Lopez-Yunez et al[159]	Retrospective, multicenter	1/50	1	0	NA
Xian et al[161]	Observational, large, multicenter registry	33	NA	1	NA
Mazya et al[111]	Observational, large, multicenter registry	24	NA	0	NA

aPTT indicates activated partial thromboplastin time; ICH, intracerebral hemorrhage; INR, international normalized ratio; mRS, modified Rankin Scale; NA, not applicable; PT, prothrombin time; sICH, symptomatic intracerebral hemorrhage; and STARS, Standard Treatment With Alteplase to Reverse Stroke.

*Elevated aPTT was defined as >39 seconds.

†One patient had a prestroke mRS score >2.

‡Elevated aPTT was defined as >37 seconds.

CONCLUSION

Therefore, the safety or efficacy of intravenous thrombolysis in patients of ACI with thrombocytopenia, INR >1.7, aPTT >40 s, or PT >15 s cannot be confirmed currently. Since the chance of discovering thrombocytopenia is rare in patients with ACI, unless there is a history of coagulopathy, it is unnecessary to check for coagulation profile before starting thrombolysis. It is not reasonable to withhold IVT and wait for the platelet count result unless there is serious suspicion of thrombocytopenia based on a patient's medical and drug history. This review study, together with the thorough review of previously published literature, provides valuable information and could lead to a revision of the exclusion criteria of IV rt-PA in ACI patients with low platelet count but otherwise eligible for thrombolysis.

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