Waiting for Platelet Counts Causes Unsubstantiated Delay of Thrombolysis Therapy

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Key Words

Platelet count • Stroke • Thrombocytopenia • Thrombolysis

Abstract

Background: Platelet counts (PCs) $<100,000/\mu\text{l}$ are considered as a contraindication for intravenous thrombolysis (IVT). While US guidelines recommend IVT initiation before the availability of clotting tests, the guidelines of the European Stroke Organization give no such practical advice. We aimed to assess the incidence of thrombocytopenia in IVT patients, outcome after thrombolysis in affected patients and the time gained by initiating treatment prior to availability of PC results. **Methods:** All patients with thrombocytopenia were identified in our prospectively acquired thrombolysis database. Baseline demographic data, intracerebral hemorrhage rates as well as functional outcome were assessed. The median time between initiation of thrombolysis and availability of PCs was calculated. **Results:** Of 625 IVT patients, 3 (0.5%) had thrombocytopenia at stroke onset. None of them developed intracerebral hemorrhage (ICH) or died during the follow-up. Waiting for PCs would have delayed treatment in 72.4% of the patients, with a median hypothetical delay of 22 min (interquartile range: 11–41 min). **Conclusions:** To date, there are no sufficient data to evaluate the

ICH risk in thrombocytopenic patients. However, thrombocytopenia is rare in IVT patients. Thus, generally waiting for PC results prior to initiation of IVT is not warranted. Avoiding this significant delay yields shorter door-to-needle times and potentially more effective treatment.

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Introduction

Based on randomized controlled trials [1, 2], European and US guidelines consider thrombocytopenia defined as platelet count (PC) $<100,000/\mu\text{l}$ as a contraindication for intravenous thrombolysis (IVT) [3, 4]. However, this arbitrary threshold has never been systematically investigated. Data on the incidence of thrombocytopenia in stroke patients and the safety of thrombolysis in this patient subgroup are limited [5–7]. Since point-of-care tests are not regularly available to assess PCs, waiting for laboratory results might significantly delay IVT initiation. However, time to treatment is crucial for treatment efficacy [8]. Benefits of expedited IVT initiation must be weighed against the potentially increased bleeding risk in patients treated without available PCs. Regarding this issue, there are no standard treatment recommendations.

Table 1. Selected baseline characteristics, and safety and outcome parameters of 3 patients with a platelet count <100,000/ μ l

Pat. No.	Platelet count	INR	Underlying disease	Age years	Sex	Baseline NIHSS	sICH	aICH	mRS on day 90
1	59,000/ μ l	1.70	chronic alcohol abuse	65	f	14	no	no	4
2	90,000/ μ l	1.15	non-Hodgkin lymphoma	64	m	5	no	no	0
3	96,000/ μ l	1.07	–	78	m	7	no	no	4

INR = International normalized ratio; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale.

While the American Heart Association/American Stroke Association guidelines [4] recommend IVT initiation in stroke patients without suspected coagulopathy prior to obtaining clotting results including PC, European Stroke Organization (ESO) guidelines give no such practical recommendation [3]. The aim of our study was to analyze how many IVT patients initially present with PCs <100,000/ μ l and to evaluate their clinical safety and outcome parameters. Furthermore, we assessed the median time gained by initiating IVT prior to obtaining PCs.

Materials and Methods

Patient Selection, Treatment and Evaluation of Outcome

The Erlangen Stroke and Thrombolysis Database is a prospective database of all patients with acute ischemic stroke treated at the University Hospital Erlangen, Germany. We identified IVT patients with a platelet count of <100,000/ μ l on admission between 01/2006 and 12/2010. According to our institutional protocol, IVT is initiated independently of PC availability, and platelets <100,000/ μ l are no IVT contraindication. Using point-of-care tests, we immediately assessed the international normalized ratio (CoaguCheck, Roche, Germany), blood glucose (AccuCheck, Roche, Germany) and basic blood chemistry (ABL-555; Radiometer Copenhagen, Denmark). International normalized ratios >1.7 are considered an IVT contraindication [4]. General blood tests including PC are drawn on admission and sent to our central laboratory. Upon analysis, results become available via intranet. Since 01/2009, ‘hypothetical delay of treatment’ defined as time between IVT bolus and availability of PCs was prospectively introduced into the database. Since then data of a representative sample of 322 consecutive patients were available for this analysis.

Asymptomatic intracerebral hemorrhage (aICH) and symptomatic ICH (sICH) were defined using European Cooperative Acute Stroke Study III criteria [2]. PCs of patients with and without sICH were compared using the Mann-Whitney U test. On day 90, outcome was assessed using the modified Rankin Scale. Analyses were performed using SPSS software (version 18.0; SSPS Inc., Chicago, Ill., USA).

Results

Baseline Characteristics

IVT patients (n = 625) were included in the analysis. No patient who presented as IVT candidate was withheld therapy solely because of a low PC. Moreover, IVT was not stopped in any patient after PC results became available. Three (0.5%) IVT patients had baseline PCs <100,000/ μ l (table 1). Two of them had a history of diseases predisposing to thrombocytopenia (long-standing alcohol abuse or chronic lymphatic leukemia). The 3rd patient had unsuspected but only mild thrombocytopenia (96,000/ μ l). No specific cause was found during the diagnostic workup.

Median Time from Thrombolysis to Availability of PC

Waiting for PC results would have delayed treatment in 72.4% of the patients, and the median time between IVT initiation and availability of platelet counts was 22 min (interquartile range, IQR: 11–41 min).

Impact of PC on IVT Safety

None of the thrombocytopenic patients developed hemorrhage or died during the follow-up (table 1). sICH occurred in 21 (3.4%) and aICH in 41 (6.6%) of the 622 patients with normal PCs. PCs did not differ between patients with (median PC 233,000/ μ l; IQR: 198,500–283,000/ μ l) and without sICH (median 237,000/ μ l; IQR: 196,500–296,000/ μ l; p = 0.97).

Discussion

PCs <100,000/ μ l are generally considered as a contraindication for IVT according to European and US guidelines [3, 4]. This threshold has never been systematically investigated and is merely based on the exclusion criteria of the pivotal randomized controlled trials designed to

maximize treatment safety [1, 2]. US guidelines state that ‘although it is desirable to know the results of these tests (PC) before giving tissue-type plasminogen activator, thrombolytic therapy should not be delayed while awaiting the results unless there is clinical suspicion of (...) thrombocytopenia’ [4]. In contrast, ESO guidelines provide no such practical advice. Three crucial findings of our data support the American recommendation: (i) relevant thrombocytopenia is rare in IVT candidates; (ii) given this low incidence, waiting for PC results would significantly and unnecessarily delay treatment in many patients with normal PCs, and (iii) to date there are no sufficient data to evaluate the ICH risk in thrombocytopenic patients.

Several authors described thrombocytopenia in stroke patients, but information on incidence, outcome and safety in IVT patients is still limited [5–7, 9]. Cucchiara et al. [5] found unsuspected thrombocytopenia in 6/1,752 (0.3%) unselected stroke patients. They concluded from the low overall incidence, that ‘the benefit of thrombolysis may outweigh the bleeding risk of inadvertently treating a patient with thrombocytopenia’ [5]. Rost et al. [7] specifically analyzed acute stroke patients within the IVT time window. Only 1/470 (0.2%) patients had unsuspected thrombocytopenia. In contrast to our patients, none of their thrombocytopenic patients received tissue-type plasminogen activator [7]. Meretoja et al. [6] found thrombocytopenia in 7/985 (0.7%) IVT patients. Thus, in three different cohorts, rates of unsuspected thrombocytopenia were nearly identical to our results, strongly arguing for the robustness and precision of this estimate.

Waiting for PCs before IVT would have delayed treatment in 72.4% of our patients by a median of 22 min (IQR: 11–41 min). Taking into account a median door-to-needle time of 25 min at our hospital [10] this would have almost doubled time to treatment. Time to receipt of PC results is hospital specific and might be shorter in selected centers, but since thrombolysis is more effective with earlier initiation [8], any delay will cause less favorable outcomes in the majority of patients with normal PCs for the sake of avoiding potential treatment complications in very few thrombocytopenic IVT patients. To our knowledge, this is the first study to quantify the hypothetical delay caused by waiting for PC results prior to thrombolysis.

Is it even warranted to withhold thrombolysis because of mild thrombocytopenia? In general, the risk of spontaneous major bleeding does not increase significantly until PCs fall $<10,000/\mu\text{l}$ [11]. Data on the effect of PC results on IVT safety are limited, and no threshold value indicating an increased thrombolysis-related sICH risk is known. In contrast to our data, Tanne et al. [9] identified

lower PCs as a predictor for sICH. However, their analysis was restricted to patients with PCs $>100,000/\mu\text{l}$ and thus provided no information on thrombolysis in thrombocytopenic patients. In a study on off-label IVT, 1/7 patients with thrombocytopenia developed sICH [6]. No sICH was seen in our thrombocytopenic patients. However, the low thrombocytopenia incidence in all mentioned studies prevents valid conclusions on IVT safety. Furthermore, 2 of our thrombocytopenic patients had only mildly decreased PCs ($\geq 90,000/\mu\text{l}$). In some diseases (e.g. immune thrombocytopenic purpura), mild thrombocytopenia may even be associated with increased blood clotting activity [12]. This can be explained by two mechanisms: (i) increased platelet reproduction with young, functionally more active platelets in the peripheral blood, and (ii) platelet destruction with release of humoral factors and thrombogenic microparticles inducing activation of thrombin and other coagulation factors [13].

Our study has limitations, most notably the single center design. The number of IVT patients with platelet counts $<100,000/\mu\text{l}$ is small and thus the study is underpowered for safety analysis. However, given the low incidence of thrombocytopenia in IVT patients, collecting valid safety data would require very large cohorts and performing a randomized controlled trial on thrombolysis in patients with platelet counts $<100,000/\mu\text{l}$ is obviously not feasible.

Conclusions

Thrombocytopenia is very rare in IVT patients, and waiting for PCs leads to significant treatment delay in many patients with normal PCs. Avoiding this delay yields significantly shorter door-to-needle times and earlier, potentially more effective treatment. Thus, it seems unwarranted to wait for PC results before IVT initiation unless there is clinical suspicion or a history of severe thrombocytopenia. Our data support US guidelines and suggest that European guidelines should adopt this practical advice.

Disclosure Statement

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