Does Body Weight Influence the Response to Intravenous Tissue Plasminogen Activator in Stroke Patients?

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Abstract

Background: The recommended dose of IV tissue plasminogen activator (t-PA) for ischemic stroke patients weighing >100 kg (ISPW >100 kg) is fixed at 90 mg. Elevated levels of plasminogen activator inhibitor-1 (PAI-1) and impaired fibrinolysis have been reported in heavy patients, suggesting that ISPW >100 kg may require higher doses of t-PA. We hypothesized that ISPW >100 kg are less likely to benefit from IV t-PA compared to patients who weigh ≤100 kg and receive a weight-based dose. **Methods:** We queried the National Institute of Neurological Disorders and Stroke t-PA study database, and performed multivariate logistic regression analyses to analyze the effects of weight (>100 vs. ≤100 kg) and t-PA dose on functional outcomes at 3 months. **Results:** Six percent of the t-PA and 10% of the placebo cohorts had an actual body weight >100 kg. Weight >100 kg emerged as a predictor of worse outcome (OR = 5.76; p = 0.017) and neurological deterioration (OR = 3.4; p = 0.07) after t-PA. This negative impact of body weight on outcome was not seen among placebo-treated patients. We also found a trend for an association between lower doses of t-PA and unfavorable 3-month outcomes in t-PA-treated patients (OR = 1.9; p = 0.05). **Conclusions:** ISPW >100 kg seem to derive less benefit from IV t-PA than their lighter counterparts. This may be partly attributed to the use of fixed non-weight-adjusted dosing in heavier patients. The mechanism(s) underlying this observation and its potential therapeutic implications require further investigations.

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Introduction

Current guidelines for intravenous (IV) thrombolysis with tissue plasminogen activator (t-PA) after acute ischemic stroke recommend a weight-based dose of 0.9 mg/kg, up to a maximum total dose of 90 mg for any given subject [1]. As a result, ischemic stroke patients weighing >100 kg (ISPW >100 kg) receive a dose of 90 mg irrespective of their actual weight. There is little reported information on the safety and efficacy of limited versus weight-based dosing of IV t-PA in ISPW >100 kg. The choice of a limited dose of 90 mg of IV t-PA for all ISPW >100 kg is arbitrary, and largely based on the results of a pilot dose-escalation study of 7 dose tiers of IV t-PA (ranging from 0.35 to 1.08 mg/kg) in 94 patients, where 4 of 5 symptomatic intracerebral hemorrhages (ICH) occurred at a dose of 0.95 mg/kg, 1 at 0.89 mg/kg and none at doses ≤0.85 mg/kg [2–4]. While the use of a limited dose, as opposed to a weight-adjusted dose, in ISPW >100 kg might reduce the risk of ICH, it is unknown if heavier

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patients may be undertreated compared to their lighter counterparts.

Recent studies have shown that circulating levels of plasminogen activator inhibitor-1 (PAI-1), an endogenous inhibitor of plasminogen activation, are elevated in heavy individuals, and that heavy weight is associated with impaired fibrinolysis [5–7]. Taken together, we hypothesized that ISPW >100 kg may require higher doses of IV t-PA than 90 mg, and thus are less likely to benefit from t-PA compared to patients who weigh ≤100 kg and receive weight-adjusted doses. Therefore, we undertook this exploratory study to investigate the effects of body weight, dichotomized as >100 versus ≤100 kg, and t-PA dose on the 3-month clinical outcome in patients who participated in the National Institute of Neurological Disorders and Stroke (NINDS) t-PA stroke trial [8].

Patients and Methods

Baseline and Outcome Assessment
We queried the NINDS (parts 1 and 2) t-PA stroke trial using the public access data files available from National Technical Information Services. The NINDS trials were multicenter, prospective, double-blinded, placebo-controlled, randomized trials of IV t-PA for acute ischemic stroke [8]. The details of these trials have been previously published [8–10]. Briefly, the patients were randomized to receive either placebo or IV t-PA (0.9 mg per kg body weight up to a maximal dose of 90 mg for any given subject) within 3 h of stroke onset. Clinical data were collected at baseline, 24 h, 7–10 days, 3 months and 1 year after randomization. Stroke outcome on day 90 was assessed by National Institute of Health Stroke Scale (NIHSS) score, modified Rankin scale (mRS), Barthel Index (BI) and Glasgow Outcome Scale. Patients who died before the 3-month assessment were given the worst possible score for all outcomes. In cases of surviving patients with missing outcome data, outcome data obtained after 3 months were used. If there were none, the data from the measurement closest in time, but at least 7 days after randomization, were used. Otherwise, the worst possible score was assigned. In-hospital neurological deterioration was defined as an increase in the NIHSS score by ≥4 points compared to baseline [8].

We extracted the neurological status (deterioration) on days 7–10, and the BI, NIHSS, and BI at 3 months to assess for functional outcomes of both t-PA and placebo-treated patients from the NINDS dataset. For the purposes of our analysis, patients with a score of either ≥95 on the BI, ≤1 on the NIHSS, or ≤1 on the mRS at day 90 were considered to have a favorable outcome. The remaining patients were considered to have less favorable (unfavorable) outcomes. We also extracted the actual body weight, and the total dose of t-PA delivered based on estimated weight. We calculated the corrected percentage of administered dose for each t-PA-treated individual after adjusting for his/her actual body weight based on a desired total dose of 0.9 mg/kg according to the following formula: (dose delivered based on estimated weight × 100)/(actual body weight × 0.9). A corrected dose <100 was considered to represent a lower t-PA dose than desired. We also retrieved 25 demographic, clinical, laboratory and radiological variables previously shown to influence outcome after stroke or response to thrombolysis [11–15]. These included: age, sex, race, baseline NIHSS score, history of hypertension, diabetes mellitus, congestive heart failure, atrial fibrillation, atherosclerosis, hyperlipidemia, myocardial infarction, hepatic disease (since plasma clearance of t-PA results from its uptake in the liver), current smoking, alcohol use, history of prior stroke or transient ischemic attack, heparin or aspirin use prior to randomization, admission serum glucose, admission systolic and diastolic blood pressure, time from stroke onset to treatment, classification of the stroke subtype, presence of visible hypodensity on initial CT scan and hemispheric location of the infarct.

Statistical Analysis
We divided each of the placebo and t-PA cohorts into 2 subgroups (favorable vs. less favorable outcome) based on the 3-month functional outcomes (BI, NIHSS or mRS) as described above. Univariate comparisons were made between the subgroups within each cohort (using Student's t test for continuous variables, Wilcoxon's rank-sum test for nonparametric data and Fisher's exact test for categorical variables) to determine intra-cohort differences in the 25 potential predictors of functional outcome. Given the interaction between body weight and t-PA dose, we then performed 2 separate multivariate logistic regression analyses: model A to determine the effects of weight (>100 vs. ≤100 kg) on functional outcomes at 3 months in each cohort; model B to determine the effects of lower t-PA dose (corrected dose) on functional outcomes at 3 months in t-PA-treated patients. To maximize sensitivity, body weight >100 or ≤100 kg (model A) or t-PA-corrected dose (model B) and those variables with a value of p < 0.2 in univariate analyses were included into the multivariate logistic regression models, with unfavorable 3-month outcome as the dependent variable. Similar analysis was performed to determine the effects of weight (>100 vs. ≤100 kg) on neurological deterioration at 7–10 days. Predictor variables with p < 0.05 were retained in the multivariate model, and associations were presented as odds ratios (OR) with corresponding 95% confidence intervals.

Results

Twenty (6%) of the 312 t-PA patients and 32 (10%) of the 312 placebo patients had an actual body weight >100 kg. Baseline characteristics of the t-PA group are summarized in table 1. As shown, patients weighing >100 kg were younger (57 ± 10 vs. 69 ± 10; p < 0.001) and had a lower rate of atrial fibrillation (0 vs. 20%; p = 0.018) compared to their lighter counterparts. The rates of symptomatic ICH were not significantly different between patients >100 and ≤100 kg (p = 0.129). In the placebo cohort, patients weighing >100 kg were largely women (81 vs. 56%; p = 0.007). They were also younger (61 ± 11 vs. 66 ± 12 years; p < 0.014) than their lighter counterparts.

Table 1. Baseline characteristics by body weight among t-PA-treated patients

Variables	Body weight >100 kg (n = 20)	Body weight ≤100 kg (n = 292)	p value
Age, years	56.9 ± 10.6	68.7 ± 11.0	<0.001
Female	6 (30)	128 (44)	0.253
Race			0.452
White, non-Hispanic	12 (60)	193 (66)	
Black	8 (40)	72 (25)	
Others	0 (0)	27 (9)	
Baseline NIHSS score (median and range)	14 (1–37)	10 (3–28)	0.156
Rate of symptomatic ICH	3 (15)	17 (6)	0.129
Comorbid conditions			
Atrial fibrillation	0 (0)	58 (20)	0.018
Diabetes mellitus	7 (35)	61 (21)	0.163
Hypertension	16 (80)	189 (66)	0.227
Hyperlipidemia	7 (44)	70 (29)	0.256
Congestive heart failure	1 (5)	43 (15)	0.327
Myocardial infarction	7 (38)	63 (23)	0.168
Hepatic disease	0 (0)	9 (3)	1.0
Atherosclerosis	7 (41)	82 (33)	0.597
Current smoking	10 (50)	94 (33)	0.144
Alcohol use	13 (65)	137 (49)	0.173
Prior stroke	0 (0)	45 (15)	0.091
Prior TIA	3 (15)	47 (17)	1.0
Heparin use prior to baseline stroke	0 (0)	5 (2)	1.0
Aspirin use prior to randomization	8 (40)	119 (41)	1.0
Admission serum glucose, mg/dl	149 ± 74	148 ± 70	0.965
Admission systolic BP, mm Hg	153 ± 22	159 ± 19	0.255
Admission diastolic BP, mm Hg	88 ± 11	84 ± 13	0.209
Presence of hypodensity on CT	2 (11)	24 (8)	0.656
Time from onset to treatment, min	116 ± 37	119 ± 37	0.702
Left hemisphere location	13 (65)	122 (42)	0.210
Classification of the stroke subtype			0.671
Small-vessel occlusive	4 (22)	27 (9)	
Cardioembolic	5 (28)	117 (40)	
Large-vessel occlusive	3 (17)	56 (19)	

Figures in parentheses are percentages, unless otherwise indicated.
TIA = Transient ischemic attack; BP = blood pressure.

Baseline characteristics were otherwise similar between >100 and ≤100 kg patients in both cohorts.

Table 2 summarizes the results of univariate analyses in both t-PA and placebo cohorts. As it shows, white race and small vessel occlusive stroke subtype were associated with favorable outcome at 3 months, while older age, higher baseline NIHSS score, the presence of hypodensity on initial CT scan, and history of hypertension, diabetes or heart failure were associated with worse outcome 90 days after treatment with t-PA (p < 0.05). There was a trend for an association between the presence of atrial fibrillation and worse outcome after treatment with t-PA

(p = 0.081). Older age, higher baseline NIHSS score and the presence of atrial fibrillation were associated with worse outcome in the placebo group as well (p < 0.05).

Table 3 shows the results of multivariate logistic regression analyses. As model A reveals, body weight >100 kg was strongly associated with unfavorable outcome at 3 months after t-PA therapy (OR = 5.762; p = 0.017). Older age, higher baseline NIHSS score, and history of hypertension were also associated with unfavorable outcome at 3 months. The negative impact of body weight >100 kg on 3-month outcome was not seen among the placebo-treated patients (OR = 1.52; p = 0.392). In the

Table 2. Univariate predictors of clinical outcomes at 3 months

Variables	t-PA treated patients (n = 312)			Placebo (n = 312)		
	favorable outcome (n = 168)	worse outcome (n = 144)	p value	favorable outcome (n = 127)	worse outcome (n = 185)	p value
Age, years	65 ± 12	71 ± 10	<0.001	63 ± 13	68 ± 11	<0.001
Female	67 (40)	67 (47)	0.253	46 (36)	82 (44)	0.162
Race			0.030			0.831
White, non-Hispanic	121 (72)	84 (58)		80 (63)	118 (64)	
Black	37 (22)	43 (30)		36 (28)	53 (29)	
Others	10 (6)	17 (12)		11 (9)	14 (8)	
Baseline NIHSS score (median and range)	10 (1–31)	18 (3–37)	<0.001	10 (1–28)	18 (4–33)	<0.001
Hyperlipidemia	41 (28)	36 (32)	0.495	30 (29)	34 (23)	0.304
Hypertension	95 (57)	110 (79)	<0.001	77 (61)	126 (69)	0.180
Diabetes mellitus	24 (14)	44 (31)	0.001	24 (19)	39 (21)	0.668
Congestive heart failure	15 (9)	29 (21)	0.005	21 (17)	34 (19)	0.651
Atrial fibrillation	25 (15)	33 (23)	0.081	16 (13)	41 (22)	0.037
Myocardial infarction	40 (25)	30 (22)	0.586	28 (23)	33 (19)	0.466
Hepatic disease	4 (2)	5 (4)	0.736	3 (2)	6 (3)	0.744
Atherosclerosis	44 (29)	45 (4)	0.065	31 (28)	50 (31)	0.686
Current smoking	61 (37)	43 (31)	0.276	53 (42)	58 (32)	0.072
Alcohol use	89 (54)	61 (45)	0.133	68 (55)	76 (42)	0.026
Prior stroke	22 (13)	23 (16)	0.519	18 (15)	20 (11)	0.38
Prior transient ischemic attack	29 (18)	21 (16)	0.757	23 (19)	26 (15)	0.426
Heparin use prior to baseline stroke	1 (1)	4 (3)	0.184	2 (2)	4 (2)	1.000
Aspirin use prior to randomization	65 (39)	62 (43)	0.488	36 (28)	53 (29)	1.000
Admission serum glucose, mg/dl	142 ± 70	157 ± 71	0.064	145 ± 67	155 ± 85	0.261
Admission systolic BP, mm Hg	153 ± 23	155 ± 21	0.535	157 ± 27	159 ± 28	0.478
Admission diastolic BP, mm Hg	85 ± 14	85 ± 13	0.686	89 ± 18	89 ± 15	0.781
Presence of hypodensity on initial CT	8 (5)	18 (13)	0.022	15 (12)	13 (7)	0.165
Time from onset to treatment, min	118 ± 37	121 ± 38	0.537	123 ± 38	118 ± 35	0.271
Left hemisphere location	83 (49)	77 (53)	0.896	69 (54)	82 (44)	0.131
Classification of the stroke subtype			0.002			0.071
Small-vessel occlusive stroke	25 (15)	6 (4)		20 (16)	10 (5)	
Cardioembolic stroke	53 (32)	69 (49)		46 (37)	73 (40)	
Large-vessel occlusive stroke	28 (17)	31 (22)		21 (17)	45 (25)	
Body weight >100 kg	10 (6)	10 (7)	0.818	12 (9)	20 (11)	0.850

Figures in parentheses are percentages, unless otherwise indicated. BP = Blood pressure.

placebo cohort, only older age (OR = 1.04; p = 0.002) and higher baseline NIHSS score (OR = 1.21; p < 0.001) were associated with unfavorable 3-month outcome. In order to further investigate whether the observed discrepancy in the effects of body weight between placebo- and t-PA-treated patients is attributed to 'lower than desired' administered dose of t-PA, we performed an additional regression analysis (model B) to determine the effects of corrected t-PA dose on outcome. As seen in table 3 (model B), we found a strong trend for an association between lower dose of t-PA and less favorable outcome after 3 months (OR = 1.925; p = 0.050). We also found a trend for

an association between body weight >100 kg and neurological deterioration 7–10 days after treatment with t-PA (OR = 3.365; p = 0.07).

Discussion

We found an independent association between body weight >100 kg and less favorable outcomes at 3 months after acute ischemic stroke in patients who received IV t-PA, but not in the placebo cohort of the NINDS t-PA stroke study. This indicates that body weight >100 kg it-

Table 3. Logistic regression models for prediction of less favorable outcomes at 3 months

	t-PA treated patients (n = 312)		Placebo (n = 312)	
	OR	p	OR	p
Model A: by clinical, laboratory, radiological variables and body weight				
Body weight >100 kg	5.763 (1.356–24.479)	0.017	1.525 (0.581–4.004)	0.392
Hypertension	2.614 (1.177–5.804)	0.018	1.165 (0.637–2.128)	0.621
Baseline NIHSS score	1.205 (1.134–1.281)	<0.001	1.213 (1.148–1.282)	<0.001
Age	1.049 (1.010–1.090)	0.013	1.045 (1.016–1.075)	0.002
Model B: by clinical, laboratory, radiological variables and corrected dose of t-PA				
Lower dose of t-PA	1.925 (1.000–3.706)	0.050	n.a.	
Hypertension	2.318 (1.143–4.702)	0.020		
Baseline NIHSS score	1.190 (1.129–1.254)	<0.001		
Age	1.043 (1.010–1.079)	0.014		

Figures in parentheses are 95% CI.

self does not adversely affect the natural outcome after ischemic stroke, and implies that factors inherent to t-PA therapy are likely to account for the disparate effects of body weight on outcome in both cohorts. Our finding of a strong trend for an association between a lower corrected dose of t-PA and poor outcome in t-PA-treated patients suggests that lower t-PA dosing in ISPW >100 kg could play a role.

The safety and efficacy of limited versus weight-based dosing of IV t-PA in ISPW >100 kg have not been systematically studied. Previous open-label, safety, dose-escalation studies of IV t-PA in acute ischemic stroke patients reported increased risk of symptomatic ICH with doses ≥0.95 mg/kg compared with ≤0.85 mg/kg [3, 4]. These pilot observations led the investigators to propose a dose of 0.9 mg/kg, since it also had a documented efficacy in lysing coronary artery thrombi [4]. It is noteworthy that 31 patients received IV t-PA at a dose of 0.95 mg/kg in these dose-finding studies and that the total dose of t-PA varied from 53.9 to 86.6 mg, indicating that none of these patients was >100 kg. A formal dose-response interrogation was also absent for ISPW >100 kg in subsequent efficacy studies because a limited reduced dose was preselected after the set maximum of 90 mg regardless of the patient's weight [8]. Therefore, it is not known whether this limited dose can achieve adequate benefits in patients weighing >100 kg. Our analysis, with the use of corrected t-PA doses adjusted by actual body weights rather than weights estimated at the time of t-PA administration, showing a trend toward an unfavorable 3-month outcome with lower t-PA dosing suggests that decreased benefit from t-PA in

patients >100 kg could be potentially attributed to lower total dose of t-PA, relative to their body weight.

Several other factors could potentially account for the observed results. The blood concentration of t-PA in patients with body weight >100 kg may influence the effect of thrombolytics. Coagulation analysis of patients receiving IV t-PA found that the patients with lower body weight tended to have higher serum t-PA levels at the end of the infusion, and thus were more likely to experience systemic fibrinolysis [16]. Patients with body weight >100 kg might have a larger blood volume and subsequently lower plasma t-PA levels available for thrombus dissolution. Furthermore, the concentration of free active t-PA in blood and fibrinolysis in the vascular bed are regulated by the rate of secretion of t-PA, inhibition of t-PA by PAI-1 and other inhibitors, and the hepatic clearance of t-PA. Among the inhibitory factors, the rapid-acting PAI-1 is the most important [5]. Several studies have noted elevated PAI-1 levels in heavy patients [6, 16–18]. PA1-1 is partly synthesized in adipocytes, particularly in the abdominal region, and its activity is strongly related to abdominal obesity as mirrored by high waist circumference or waist-to-hip ratio [6]. High circulating levels of PAI-1 inhibit t-PA and lead to low levels of free t-PA, i.e. low t-PA activity and impaired capability of thrombolysis. In plasma, PAI-1 forms stable stoichiometric complexes with t-PA. As PAI-1 levels rise in the blood, the fraction of t-PA in the active form falls and t-PA/PAI-1 complex levels rise [19]. Furthermore, the clearance of total t-PA in the blood (active t-PA plus t-PA/PAI-1 complex) becomes slower with higher levels

of PAI-1. As a result, the activity of free t-PA declines. Interestingly, a recent study found that nutritionally induced and genetically determined obesity has a deleterious effect on the outcome of thrombotic ischemic stroke in mice, and that the negative effect of obesity correlated with elevated levels of PAI-1 and was not seen in PAI-1-deficient obese mice [20]. Results from the Framingham Offspring Study also showed a direct association between the body mass index (BMI) and prothrombotic factors, including fibrinogen, factor VII and PAI-1 [6]. Overweight and obesity are often defined in terms of the BMI, which is calculated as: weight (kg)/[height (m)]^2. The WHO-based classification indicates that adults with BMI 25–29.9 are considered overweight and ≥ 30 are obese [21]. Therefore, although a body weight >100 kg does not necessarily imply obesity, a stroke patient who weighs 100 kg and is less than 2 m (6.6 ft) tall is almost always considered overweight or obese. It is, thus, conceivable to hypothesize that the observed association between body weight >100 kg and less favorable outcome after treatment with IV t-PA could be the result of impaired fibrinolysis and increased resistance to thrombolysis as a result of higher levels of circulating PAI-1 in these patients. Plasma levels of PAI-1 or t-PA levels after IV infusion were not assessed in the NINDS trials. Future prospective analyses are required to adequately evaluate the impact of body weight on these parameters and response to IV t-PA.

Previous studies implicated age and severity of neurological deficit assessed by NIHSS as predictors of poor outcome [22, 23]. Our results are concordant with earlier reports. We also found that history of hypertension is associated with less favorable outcome after t-PA. There are several speculative mechanisms by which chronic hypertension could negatively impact clinical outcomes. However, it is unclear why the effect of hypertension was seen among t-PA treated patients, but not the placebo cohort. This finding requires further investigation.

Older age and atrial fibrillation emerged as predictors of worse outcome in univariate analyses. However, the t-PA-treated patients weighing >100 kg were 12 years younger than their lighter counterparts, and none had atrial fibrillation. This suggests that the observed effect of body weight >100 kg on outcome after treatment with IV t-PA is unlikely to be affected by these confounders, and is likely underestimated.

It must be emphasized that our study is exploratory, and as such is appropriate for hypothesis generation rather than hypothesis testing. Furthermore, our findings should be interpreted with caution given the linear estimates of t-PA dosing and nonlinear kinetics of t-PA infusion. There are other limitations to our study. First, our analysis was retrospective in nature, and the number of patients with body weight >100 kg was small. We were unable to examine other large IV t-PA trials cohorts and were only able to examine the NINDS cohort because the data are publicly available. It is, therefore, important to confirm our findings in other large IV t-PA stroke registries, and to construct a prospective centralized database to systematically collect data for stroke patients >100 kg. Second, we did not have angiographic data to determine recanalization rates in response to t-PA, or laboratory measures of serum levels of t-PA, PAI-1 or other prothrombotic factors. Lastly, we did not have available data on the use of pharmacological agents which mediate overexpression of PAI-1, such as insulin, glucocorticoids and angiotensin II [7, 24–26]. Only a well-designed prospective study can address these limitations.

Our findings, albeit preliminary and hypothetical, could have important clinical implications, and warrant further investigations to determine the safety and efficacy of limited versus alternative weight-based IV t-PA dosing in patients with body weights greater than 100 kg. It is worth noting that the use of weight-based dosing for patients >100 kg does not necessarily imply higher risk of hemorrhagic complications. A retrospective analysis of the factors associated with ICH after IV t-PA for ischemic stroke found that while doses ≥ 0.95 mg/kg significantly increased the risk of ICH, there was no relationship between the total dose of t-PA (in milligrams) and ICH risk [2]. Furthermore, lighter patients seemed more likely to develop ICH after t-PA than heavier ones [2].

In conclusion, we found that ISPW >100 kg, who receive a limited dose of IV t-PA, tend to have poor outcomes after treatment compared with their lighter counterparts who receive a weight-based dose at 0.9 mg/kg. This seems to be partly attributed to a lower dose of t-PA per body weight in ISPW >100 kg. Future studies with weight-adjusted IV t-PA dosing in ISPW >100 kg are warranted, and further investigations are required to better define the exact mechanism(s) underlying our observation.

Acknowledgments

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