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Outcome of Intravenous Thrombolysis in Stroke Patients Weighing over 100 kg

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Key Words
Ischemic stroke · Tissue plasminogen activator · Overweight · Clinical outcome

Abstract
Background: Intravenous thrombolysis with alteplase for ischemic stroke is fixed at a maximal dose of 90 mg for safety reasons. Little is known about the clinical outcomes of stroke patients weighing >100 kg, who may benefit less from thrombolysis due to this dose limitation. ***Methods:*** Prospective data on 1,479 consecutive stroke patients treated with intravenous alteplase in six Swiss stroke units were analyzed. Presenting characteristics and the frequency of favorable outcomes, defined as a modified Rankin scale (mRS) score of 0 or 1, a good outcome (mRS score 0–2), mortality and symptomatic intracranial hemorrhage (SICH) were compared between patients weighing >100 kg and those weighing ≤100 kg. ***Results:*** Compared to their counterparts (n = 1,384, mean body weight 73 kg), patients weighing >100 kg (n = 95, mean body weight 108 kg) were younger (61 vs. 67 years, p < 0.001), were more frequently males (83 vs. 60%, p < 0.001) and more frequently suffered from diabetes mellitus (30 vs. 13%, p < 0.001). As compared with patients weighing ≤100 kg, patients weighing >100 kg had similar rates of favorable outcomes (45 vs. 48%, p = 0.656), good outcomes (58 vs. 64%, p = 0.270) and mortality (17 vs. 12%, p = 0.196), and SICH risk (1 vs. 5%, p = 0.182). After multivariable adjustment, body weight >100 kg was strongly associated with mortality (p = 0.007) and poor outcome (p = 0.007). ***Conclusion:*** Our data do not suggest a reduced likehood of favorable outcomes in patients weighing >100 kg treated with the current dose regimen. The association of body weight >100 kg with mortality and poor outcome, however, demands further large-scale studies to replicate our findings and to explore the underlying mechanisms.

Introduction

Intravenous thrombolysis (IVT) with alteplase is currently the only approved treatment for acute ischemic stroke. The international stroke guidelines recommend a weight-adapted dose (0.9 mg alteplase per kilogram body weight) and a maximum dose of 90 mg for safety reasons [1, 2], meaning that no further dose adjustment is permitted in patients weighing >100 kg. However, this recom-

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mendation is based on few small dose escalation studies [3, 4]. On the other hand, obesity has recently risen to epidemic levels and the World Health Organization estimates that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese [5]. Keeping in mind that obesity is an independent predictor of ischemic stroke [6, 7], obese patients will constitute an increasing group of candidates for IVT. Furthermore, several studies reported an elevated level of plasminogen activator inhibitor-1 and impaired fibrinolysis in obese patients [8, 9]. Thus, stroke patients weighing >100 kg may benefit less from IVT, which may have major therapeutic implications in clinical practice. We present the outcomes of patients weighing >100 kg compared with those weighing ≤100 kg after IVT for acute ischemic stroke.

Methods

We studied prospectively collected data of consecutive patients with acute ischemic stroke who underwent IVT at six Swiss stroke centers up to December 31, 2008. The Appendix provides detailed data about the number of patients and the study period for each center. Baseline investigations included neurologic and physical examination, assessment of stroke severity by using the National Institutes of Health Stroke Scale (NIHSS) [10], routine blood analysis, 12-lead electrocardiography, brain computed tomography and/or magnetic resonance imaging. The following variables were ascertained: age, gender, baseline NIHSS score, vascular risk factors according to predefined criteria [11], history of coronary heart disease, antithrombotic medication, time to treatment, stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [12], blood pressure and blood glucose values. Body weight was measured by the unit nurse on admission or, when not feasible, obtained verbally from the patient or caregiver. Thrombolysis was applied according to current guidelines using intravenous alteplase 0.9 mg/kg to a maximum of 90 mg; 10% of the total dose was given as a bolus and the remaining dose within the next hour [1, 2]. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 h. Follow-up CT or MRI was obtained 24–48 h after IVT and additional scans in case of clinical deterioration. Functional outcome was assessed by outpatient visits or structured telephone interviews using the modified Rankin Scale (mRS) [13].

Outcome Measurements

The primary outcome measure was the incidence of a favorable outcome at 3 months, defined as a mRS score of 0 or 1. We additionally evaluated the incidence of a good outcome, defined as an mRS score of 0–2. Secondarily, we assessed the mortality rate at 3 months and the rate of symptomatic intracranial hemorrhage (SICH) using both the National Institutes of Neurological Diseases and Stroke (NINDS) and European-Australasian Acute Stroke Study (ECASS) II criteria [14, 15].

Statistical Analysis

Nonnormally distributed data were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. The distribution of frequencies was examined using the χ^2 test or Fisher's exact test where appropriate (the latter if some expected counts in the two-by-two table were less than 5). The influence of body weight (>100 vs. ≤100 kg) on the outcomes was examined using univariate analysis. Multivariable logistic regression analyses were performed to assess joint effects of body weight and other predictors on the outcomes. Selection of parameters was based on clinical criteria and was derived from the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST) registry that evaluates outcome predictors [16]. Thus, the following variables were introduced into the model: baseline NIHSS score, age and blood glucose for all 3 outcome measures; additionally, gender and diastolic blood pressure for a favorable outcome and mortality, and antiplatelet medication and systolic blood pressure for SICH. Significance was fixed at $p < 0.05$.

Results

Study Population

Among 1,503 stroke patients treated with IVT, 1,479 (98%) were eligible for this study; 24 patients (2%) were excluded because of lacking body weight data. Of the included 1,479 patients, 95 (6.4%) had a body weight >100 kg [range 101–150 kg, mean 107.5 ± 9.3 kg, median 103.0 kg (95% CI 105.6–109.4), IQR 103–110 kg] and 1,384 (93.6%) had a body weight ≤100 kg [range 36–100 kg, mean 73.1 ± 11.6 kg, median 74.0 kg (95% CI 72.4–73.7), IQR 66–80 kg]. The maximum dose of alteplase was 90 mg.

As compared with their counterparts, patients weighing >100 kg were younger (61 vs. 67 years of age, $p < 0.001$) and more often men (83 vs. 60%, $p < 0.001$) with a higher rate of diabetes mellitus (30 vs. 13%, $p < 0.001$) (table 1). Stroke severity assessed by the baseline NIHSS score, time to treatment, blood pressure, antithrombotic medication and stroke causes were comparable in the two cohorts (table 1).

Outcome

At 3 months, clinical outcome was available in 1,462 (99%) and classification of SICH in 1,454 (98%) of the included 1,479 patients. All patients who were lost to follow-up and all but 1 with undefined hemorrhage classification had body weights ≤100 kg.

Favorable outcomes were observed in 694 of 1,462 (47%) patients. The rates of patients with favorable outcomes at 3 months were comparable between the two groups (45.3% of patients weighing >100 kg and 47.6% of

Table 1. Baseline characteristics of alteplase-treated stroke patients with body weights >100 versus ≤100 kg

	Weight >100 kg (n = 95)	Weight ≤100 kg (n = 1,384)	p value
Male sex, n (%)	79/95 (83.2)	827/1,383 (59.8)	<0.001
Median age, years	60.1 (53.0–69.4)	70.0 (58.9–78.0)	<0.001[1]
Hypertension, n (%)	69/95 (72.6)	882/1,384 (63.7)	0.080
Current smoking, n (%)	32/95 (33.7)	369/1,383 (26.7)	0.138
Diabetes mellitus, n (%)	28/95 (29.5)	185/1,383 (13.4)	<0.001
Hypercholesterolemia, n (%)	42/83 (50.6)	611/1,353 (45.2)	0.334
Antiplatelet medication at stroke onset, n (%)	36/95 (37.9)	474/1,380 (34.3)	0.482
Anticoagulation at stroke onset, n (%)	3/95 (3.2)	37/1,380 (2.7)	0.740[2]
Coronary heart disease, n (%)	18/95 (18.9)	250/1,382 (18.1)	0.834
Median NIHSS score	12.0 (6–16)	12.0 (7–17)	0.330[1]
Median OTT, min	170.0 (135.0–180.0)	157.5 (130.0–180.0)	0.575[1]
Median SBP, mm Hg	151.0 (140.0–174.0)	155.0 (139.5–173.0)	0.645[1]
Median DBP, mm Hg	86.0 (80.0–100.0)	89.0 (79.0–100.0)	0.970[1]
Median blood glucose, mmol/l	6.5 (5.7–8.3)	6.4 (5.6–7.4)	0.088[1]
Cause of stroke			
Large artery disease, n (%)	27/95 (28.4)	333/1,378 (24.2)	
Cardiac embolism, n (%)	32/95 (33.7)	500/1,378 (36.3)	
Small artery disease, n (%)	3/95 (3.2)	64/1,378 (4.6)	0.789
Other determined etiology, n (%)	6/95 (6.3)	112/1,378 (8.1)	
Undetermined etiology, n (%)	27/95 (28.4)	369/1,378 (26.8)	

Unless otherwise indicated, figures in parentheses are IQRs. p values are calculated with the χ^2 test, unless otherwise indicated. OTT = Onset-to-treatment time; SBP = systolic blood pressure; DBP = diastolic blood pressure. [1] Mann-Whitney test. [2] Fisher's exact test.

Table 2. Outcomes in patients weighing >100 kg compared with those weighing ≤100 kg

	Unadjusted analysis				Adjusted analysis[1]	
	weight >100 kg, n	weight ≤100 kg, n	odds ratio and 95% CI	p value	odds ratio and 95% CI	p value
Favorable outcome, mRS 0–1	43/95 (45.3%)	651/1,367 (47.6%)	0.909 (0.599–1.381)	0.656	0.715 (0.422–1.213)	0.213
Good outcome, mRS 0–2	55/95 (57.9%)	874/1,367 (63.9%)	0.776 (0.509–1.183)	0.270	0.462 (0.265–0.807)	0.007
Mortality	16/95 (16.8%)	168/1,367 (12.3%)	1.445 (0.825–2.533)	0.196	2.640 (1.305–5.341)	0.007
SICH, NINDS definition	1/94 (1.1%)	73/1,360 (5.4%)	0.190 (0.026–1.379)	0.0842	0.303 (0.041–2.251)	0.243
SICH, ECASS II definition	1/94 (1.1%)	62/1,360 (4.6%)	0.225 (0.031–1.642)	0.182[2]	0.372 (0.049–2.790)	0.336

p values apply to χ^2 tests, unless otherwise indicated. Figures shown in parentheses are 95% CIs, unless otherwise indicated. [1] Adjusted for baseline NIHSS score, age, gender, blood glucose, diastolic blood pressure (favorable outcome, good outcome, mortality); baseline NIHSS score, age, blood glucose, antiplatelet medication and systolic blood pressure (SICH). [2] Fisher's exact test.

patients weighing ≤100 kg, p = 0.656). After multivariable adjustment, age ($p < 0.001$), baseline NIHSS score ($p < 0.001$) and blood glucose ($p < 0.001$) predicted a favorable outcome, while no association with body weight >100 kg was evident (p = 0.213) (table 2). Good outcomes were observed at similar frequencies in patients weighing ≤100 kg and those weighing >100 kg (63.9 vs. 57.9%, p = 0.270) (fig. 1). However, multivariable adjustment revealed an independent association between good outcome and body weight ≤100 kg (p = 0.007) (table 2).

Death within the 3-month follow-up occurred in 184 of 1,462 (13%) patients, and tended to be more frequent in patients weighing >100 kg (16.8 vs. 12.3%, p = 0.196). Multivariate logistic regression analyses identified body

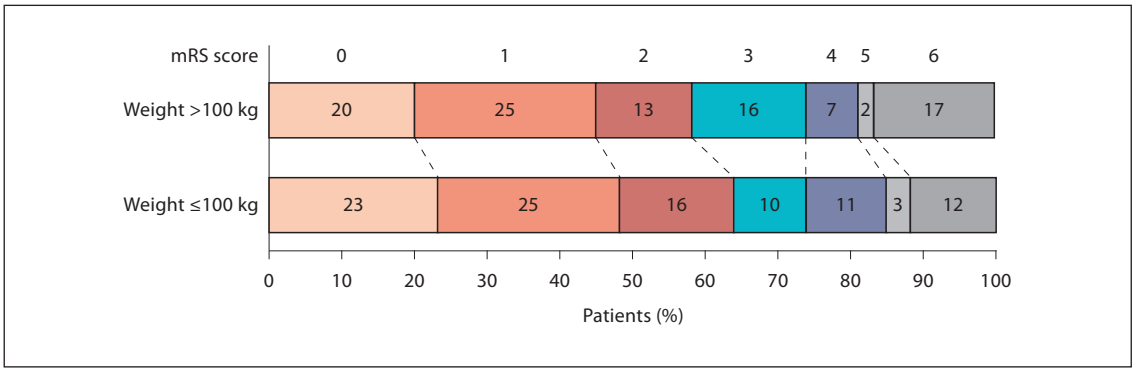

Fig. 1. Proportion of patients with body weights >100 kg versus ≤100 kg according to the mRS score at 3 months.

weight >100 kg as an independent predictor of mortality ($p = 0.007$), along with age ($p < 0.001$), baseline NIHSS score ($p < 0.001$), blood glucose ($p < 0.001$) and diastolic blood pressure ($p = 0.029$) (table 2). Sixteen patients weighing >100 kg died during the 3-month follow-up (median at day 6 after stroke onset): 15 of 16 patients were males, median age 66 years with a median baseline NIHSS score of 15. The following causes of death were identified in these 16 patients: malignant middle cerebral artery infarct (n = 6), cardiopulmonary arrest (n = 5), extensive basilar artery infarct (n = 1), second ischemic stroke (n = 1) and aspiration pneumonia (n = 1). The remaining 2 patients died in external rehabilitation centers and the exact causes of death were not identifiable.

Seventy-four of 1,454 (5%) patients experienced SICHs according to NINDS criteria, 1.1% of patients weighing >100 kg and 5.4% in the counterpart group ($p = 0.084$) (table 2). The rate of SICHs using the ECASS II criteria did not significantly differ between the two groups either (1.1 vs. 4.6%, $p = 0.182$) (table 2). Multivariate logistic regression analyses identified baseline NIHSS score as an independent predictor of SICH according to NINDS criteria ($p = 0.045$) and ECASS II criteria ($p = 0.020$) but not body weight >100 kg ($p = 0.243$ and $p = 0.336$, respectively) (table 2).

Discussion

This study aimed to assess the clinical outcomes of patients weighing >100 kg receiving intravenous alteplase fixed at 90 mg compared with patients weighing ≤100 kg, treated with weight-adapted doses of alteplase. The rates of favorable outcomes at 3 months were similar in the two groups, but an inverse association was observed with body weight >100 kg and probability of a good outcome. Several aspects have to be considered when interpreting these findings: one hypothesis might be that the worse outcome in patients weighing >100 kg may be related to the lower corrected dose of alteplase in this group. The rather low mean body weight of 107.5 kg, which exceeds the weight cutoff (100 kg) by less than 10%, may have hampered our ability to detect additional differences in favorable outcome. A further, rather theoretical reason for the divergent outcomes (favorable vs. good outcome) could be the assumption that patients weighing >100 kg may be more handicapped by slight deficits due to overweight and associated challenges as compared to lean patients. In line with our findings, Lou and Selim [17] analyzed data from the NINDS trial and suggested less benefit of IVT in stroke patients weighing >100 kg as compared with their lighter counterparts. Lower levels of plasma tissue plasminogen activator and/or higher plasma levels of plasminogen activator inhibitor-1 have been reported as a potential reason for differences in outcome [8, 17, 18]. On the other hand, however, one should be cautious not to overestimate our results in view of our observational study design and the small size of the cohort of patients weighing >100 kg. As a consequence, further large-scale studies should be performed to replicate our findings and explore the underlying mechanisms in view of potential therapeutic implications.

We are aware of mainly three studies targeting at higher alteplase doses for ischemic stroke. In two open-label dose escalation studies preceding the NINDS trial, 32 of 94 stroke patients were treated with an alteplase dose >0.9

mg/kg (31 patients received 0.95 mg/kg, 1 patient received 1.08 mg/kg) [3, 4, 14]. However, the maximal dose administered in the two studies was 86.6 mg. In the ECASS I trial, an alteplase dose of 0.95 mg/kg was used while the maximum dose was limited to 100 mg [19]. However, no data were reported on the number and outcome of patients receiving alteplase doses >90 mg. Thus, we are not aware of studies that proved and reported harm following alteplase doses exceeding the current limit of 90 mg in ischemic stroke. The dose of alteplase for myocardial infarction is limited to 100 mg [20]. These data indicate that the upper dose limit of alteplase of 90 mg seems to be more or less arbitrary.

Another finding of this study is the higher mortality in patients weighing >100 kg despite their significantly younger age as compared with their counterparts weighing ≤100 kg and the correlation of body weight >100 kg with mortality in the multivariate logistic regression analysis. The vast majority of patients weighing >100 kg who died were males (94%) and death occurred early, at a median of 6 days after stroke onset. Leading causes of death were malignant ischemic infarct and cardiopulmonary arrest whereas no fatal SICH was observed in these patients. Obesity is associated with a higher body weight, and several long-term studies reported higher mortality rates in obese patients after ischemic stroke [21–24]. It has been shown that obese stroke patients are more often prone to deep venous thrombosis [25], and other medical complications such as pneumonia or cardiovascular ischemic events appear to occur more frequently in obese patients [21–23]. These findings do not explain our results completely, however, because body weight >100 kg does not always imply obesity as is the case in some athletes. Lou and Selim [17] did not report on mortality in their study, thus no comparison with the current literature is available. Nonetheless, the increased mortality observed in patients weighing >100 kg warrants further large-scale studies to replicate our findings and explore the mechanisms as especially younger male stroke patients seem to be overweight, and these patients probably will represent a growing subgroup in the future with respect to the rapidly growing incidence of obesity. An increase in alteplase doses seems to be less promising as no randomized controlled IVT trial has established that administration of larger doses of alteplase decreases mortality after ischemic strokes. The incidences of SICH (using both NINDS and ECASS II criteria) did not significantly differ between the two body weight groups.

This study has some limitations. The observational design and the lack of a control group did not enable us to judge the efficacy of alteplase doses in patients weighing >100 kg. The cohort of patients weighing >100 kg was small, thus the possibility of a type II error cannot be excluded. We could not assess the causes of death in patients weighing ≤100 kg and thus are not able to explain the increased mortality in patients weighing >100 kg completely. Measurement of plasma plasminogen activator concentration and assessment of the body mass index of patients of varying weights might have been more appropriate. Other factors, such as liver function, age or body surface area, might have additionally influenced the pharmacokinetics of alteplase plasma concentration [26–28]. Body weight was in part self-reported by patients or caregivers. Measurement of body weight could probably be more accurate [29] although self-reported body weights have been reported to be valid in participants of the Nurses' Health Study II [30]. Finally, we did not evaluate imaging findings, such as early infarct signs, vessel occlusion or early recanalization, which might have influenced the outcomes as well.

In conclusion, our data do not suggest a reduced likelihood of favorable outcomes in patients weighing >100 kg, treated with the current dose regimen. The association of body weight >100 kg with mortality and a poor outcome, however, demands further large-scale studies to replicate our findings and explore the underlying mechanisms.

Disclosure Statement

The authors have no disclosures to report.

Appendix

Participating centers (number of patients, study period) and contributors in alphabetical order:

University Hospital of Basel (359, 10 years): S.T. Engelter, P.A. Lyrer; University Hospital of Bern (90, 9 years): M. Arnold, H.P. Mattle; University Hospital of Lausanne (298, 8 years): P. Michel, C. Odier; Cantonal Hospital of Münsterlingen (100, 9 years): F. Müller; Cantonal Hospital of St. Gallen (219, 5 years): P. Siebel, B. Weder; University Hospital of Zurich (437, 10 years): R.W. Baumgartner, D. Georgiadis, H. Sarikaya.

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