The Weight of Tissue Plasminogen Activator Dose in Overweight Patients With Strokes

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Obesity is a widespread problem, particularly in the cardiovascular disease and stroke population. The combination of hypertriglyceridemia, glucose intolerance, and inflammation is linked with increased production of the primary inhibitor of endogenous thrombolysis, plasminogen activator inhibitor-1, leading to deficient thrombolysis in overweight patients. Enhanced fibrin crosslinking has been shown to be, at least partially, responsible for delayed clot lysis among obesees. Moreover, body mass index was directly associated with fibrinogen, Factor VII, plasminogen activator inhibitor-1 and tissue plasminogen activator (tPA) antigen, von Willebrand factor, and viscosity. In contrast, body mass index itself had no impact on in-hospital mortality in patients undergoing primary percutaneous coronary interventions for acute myocardial infarction. Obese patients with acute myocardial infarction have a lower risk for in-hospital, 6-month, and 12-month mortality and cardiovascular events than patients with a normal body mass index.1 This “obesity paradox” may be explained by the fact that obese patients were younger at presentation.

tPA dose for stroke (0.9 mg/kg alteplase, maximum 90 mg) was chosen based on small dose-escalation studies. This body weight-based dose has become the standard of care after showing a significant benefit in randomized controlled trials. However, patients with stroke weighing >100 kg may theoretically receive a lower dose per kilogram than the recommended for stroke treatment, and therefore response to thrombolytic may be hampered a priori due to an insufficient tPA dose. In this issue of Stroke, Diedler et al2 shed some light onto the knowledge of one of the dark edges of stroke thrombolysis, exploring whether the 90-mg dose limit of intravenous tPA in patients weighing >100 kg is translated into a similar response to thrombolysis than those <100 kg. The authors analyzed patients weighing >100 kg and <100 kg from the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Registry (SITS-ISTR) database. Major neurological improvement, as a surrogate marker of recanalization, and 3-month outcome were comparable in both groups. In contrast, overweight patients had a higher rate of symptomatic intracranial hemorrhage and mortality than the <100-kg group. Therefore, they conclude that the current dose limit should not be modified, because despite the lower dose of tPA per kilogram and the increased risk of symptomatic intracranial hemorrhage in overweight patients, it is associated with a similar long-term outcome.

These observations are in contrast with a previous study showing that tPA underdosing is associated with poor clinical outcome.3 However, in the Diedler et al study, patients >100 kg exhibited a different baseline clinical profile, because they were more frequently male, younger, had less severe strokes, and a higher proportion of lacunar strokes compared with those <100 kg. Although after adjusting for these variables, both early- and long-term clinical outcome were similar in <100-kg and >100-kg patients, the impact of tPA underdosing in comparable older, more severe overweight patients with larger clot burden would be certainly different. Age and stroke severity are the strongest predictors of good outcome in thrombolytic treatment, and paradoxically even with a median of National Institutes of Health Stroke Scale score 2 points lower and being 8 years younger, these patients had a significantly higher mortality rate and comparable outcome to older and more severe patients. Furthermore, these patients have a higher rate of symptomatic intracranial hemorrhage, which is unexpected in young patients with less severe strokes.

The relatively low response and high mortality after thrombolysis in overweight patients is probably associated with their comorbidity. These patients had a higher proportion of risk factors and at stroke presentation were more prone to have hyperglycemia and high blood pressure. Metabolic syndrome has been identified as a predictor of poor outcome after systemic thrombolysis. Comorbidity and maybe suboptimal blood pressure control may account for the increased risk of symptomatic intracranial hemorrhage in patients >100 kg despite lower tPA dose.

The authors also support the upper dose limit of tPA because they assume that recanalization rates were comparable based on the degree of major neurological improvement in both groups. The problem is that higher proportions of patients in the overweight group had lacunar strokes, and in this stroke subtype, the use of major neurological improvement as a surrogate marker of recanalization is questionable. Therefore, further studies are required to evaluate the effects of different per kilogram doses of tPA—and novel thrombolytics—on arterial recanalization using noninvasive neurovascular techniques.

How many of our tPA-treated patients actually receive the “full” standard 0.9-mg/kg dose? In 85% of patients in this series, the weight was estimated. It has been recently dem-
onstrated that up to 40% of health professionals estimate the patient’s weight erroneously. Alteplase has a narrow therapeutic range and, therefore, a strict dosing regimen is required. Efforts should be addressed to avoid standard eyeballing body weight—and tPA dose—estimation. The use of anthropometric measurements or beds equipped with calibrated scales may reduce the likelihood of tPA misdosing in the vast majority of patients with stroke weighing <100 kg.

In conclusion, the article by Diedler and colleagues opens an interesting debate about tPA dosing in overweight patients and whether the high dose limit could hamper treatment in these groups of patients. A randomized study comparing the 90-mg dose with the 0.9 mg/kg without a higher limit in patients weighing >100 kg using arterial recanalization as a direct marker of efficacy is needed.

Disclosures
None.

References

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