LETTER TO THE EDITOR

Intravenous thrombolysis for ischaemic strokes: a call for reappraisal

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Sir,

Balami et al. (2013) state that intravenous tissue plasminogen activator thrombolysis is beneficial for the treatment of acute ischaemic stroke and that strokes are now a treatable medical emergency. A critical analysis of the data, however, raises doubts about the expansive claims of efficacy made by them and others (Wardlaw et al., 2012). The aim of tissue plasminogen activator treatment is lysis of the thrombus and recanalization of occluded cerebral arteries, to promptly restore blood flow. To prove therapeutic efficacy of the administered thrombolytic agent, angiographic demonstration of arterial recanalization is critically important as it is the only way, in patients, to conclusively demonstrate that clot lysis has occurred.

The most accurate tests to assess recanalization

Arterial recanalization has been assessed using different methods: transcranial Doppler studies, magnetic resonance angiography, CT angiography or conventional catheter angiography. However, these tests have widely variable accuracy and reliability. Conventional catheter angiography is the reference standard because of its superb accuracy for imaging evaluation of arteries. Although transcranial Doppler studies have been frequently used to determine recanalization frequency (Alexandrov et al., 2001, 2004; Demchuk et al., 2001; Molina et al., 2001; Ribo et al., 2006; Saqqur et al., 2007) their accuracy in assessing steno-occlusive disease is suboptimal and less than either CT angiography or magnetic resonance angiography studies (Feldmann et al., 2007; Jauch, 2013). Time of flight magnetic resonance angiography (Neumann-Haefelin et al., 2004; Davis et al., 2008; Marks et al., 2008; Kimura et al., 2009) is limited by loss of flow signal intensity in stenotic regions (Bash et al., 2005; Cloft, 2005; Jauch, 2013). Overall, CT angiography has a much higher specificity and sensitivity (98% compared to 70% for magnetic resonance angiography) and is recommended over both magnetic resonance angiography and transcranial Doppler studies (Bash et al., 2005; Jauch, 2013).

Therefore, unlike all previous analyses (such as Rha and Saver, 2007; Balami et al., 2013) the frequency of early recanalization is best assessed by (i) only including the results from the most accurate tests: CT angiography and conventional angiographic studies; and (ii) only including studies in which serial angiograms have been done; the first soon after stroke onset to demonstrate an arterial occlusion and a follow-up angiogram within 24 h (as the duration of action of tissue plasminogen activator is a few hours) to determine if recanalization has been achieved. All studies from a PubMed search that fulfilled these criteria have been included in this analysis.

Spontaneous improvement

Before the efficacy of intravenous thrombolytic therapy in recanalizing occluded arteries can be assessed, a direct and reliable estimate of the frequency of spontaneous clinical improvement and spontaneous recanalization is needed. Spontaneous clinical improvement in patients with ischaemic stroke implies spontaneous clot lysis and restoration of blood flow to the ischaemic territory (although instantaneous retrograde pial collateral flow may occasionally contribute to improvement). Rapid spontaneous improvement is not uncommon. Spontaneous clinical improvement to varying degrees, within 24 h of stroke onset, has been reported in 12%, 27% or 52% of patients in different studies (Biller et al., 1990; Wityk et al., 1994; Toni et al., 1998). Considering these studies together, spontaneous improvement within 24 h has been documented in 45 (27.6%) of 163 ischaemic stroke patients.
Spontaneous arterial recanalization in ischaemic stroke patients

Spontaneous recanalization within 24 h has been shown to occur in 8 (32%) of 25 (Eilaghi et al., 2013); 11 (18%) of 59 (Furlan et al., 1999); or 2 (16.7%) of 12 ischaemic stroke patients (Mori et al., 1992). In an elegant older study of patients with acute cerebral infarcts with angiographically demonstrated arterial occlusions secondary to suspected embolism, 8 (47%) of 17 patients showed spontaneous recanalization, albeit within 100 h of onset (Dalal et al., 1963).

An additional factor to consider is that ~10–25% of patients with acute ischaemic strokes do not have any evidence of arterial occlusion on angiography (Fieschi et al., 1989; Fischer et al., 2005). These include patients with lacunar infarcts with small vessel occlusion that cannot be visualized angiographically, but also patients in whom spontaneous recanalization has already occurred by the time the first post-stroke angiogram is done. The frequency of spontaneous recanalization, within 24 h, may therefore be even higher than the reported 17–32%.

Angiographically confirmed arterial recanalization after intravenous tissue plasminogen activator treatment

Balami et al. (2013) refer to a previous meta-analysis (Rha and Saver, 2007) that states that spontaneous recanalization occurred in 24% of ischaemic stroke patients and recanalization increased to 46% after intravenous tissue plasminogen activator treatment. However these and other studies (Lинфante et al., 2002) include less accurate transcranial Doppler or magnetic resonance angiography studies in their analysis. When the analysis is restricted to recanalization demonstrated by serial CT angiography or conventional angiographic studies, the recanalization rates, within 24 h after intravenous thrombolyis (21.3–57.1%) are not unequivocally better than those seen after spontaneous recanalization (17–32%), or what would be expected, considering the rates of spontaneous clinical improvement (12–52%).

Considering all studies together, after intravenous tissue plasminogen activator treatment, partial and complete recanalization within 24 h has been reported in 210 (42.4%) of 495 treated patients (del Zoppo et al., 1992; Mori et al., 1992; Lee et al., 2007; Bhatia et al., 2010; Eilaghi et al., 2013; Yeo et al., 2013). In three of these six studies the recanalization rates within 24 h of intravenous tissue plasminogen activator infusion was only 21.3%, 22.6% and 30.1% of treated patients, respectively (del Zoppo et al., 1992; Lee et al., 2007; Bhatia et al., 2010). Although it has been suggested that tissue plasminogen activator is more effective in lysing clots in smaller arteries, recanalization of more distal middle cerebral artery branches (M2 and M3) was still quite low at 27.3%, 30.8% and 38.1% of all treated patients (del Zoppo et al., 1992; Lee et al., 2007; Bhatia et al., 2010). It is emphasized that these recanalization rates, within 24 h of treatment, are similar or even less frequent than the reported frequency of spontaneous recanalization within 24 h (17–32%) (Mori et al., 1992; Furlan et al., 1999; Eilaghi et al., 2013).

Three studies have reported higher recanalization rates after treatment (47–57.1%) (Mori et al., 1992; Eilaghi et al., 2013; Yeo et al., 2013), but it should be noted that the recanalization rates reported include both partial and complete recanalization. However partial recanalization can span a wide spectrum from minimal anterograde flow to substantial reperfusion (Wintermark et al., 2013). Furthermore, even when complete recanalization occurs, tissue perfusion may still not occur in some patients, due to distal emboli or no reflow into the infarcted area because of oedema or microvascular damage (Wintermark et al., 2013). One study reported no reperfusion, despite vessel recanalization, in 12.2% of cases (Eilaghi et al., 2013). Tissue reperfusion of the downstream territory, therefore, is likely to be even less frequent than the recanalization rates reported.

Thus, although larger number of patients need to be studied, the most accurate serial angiographic evidence available suggests that intravenous tissue plasminogen activator may not be an effective treatment for ischaemic strokes. Early post-stroke recanalization and reperfusion, observed in some patients, is most likely spontaneous.

Reliability of post-stroke functional studies

As evidence of efficacy, Balami et al. (2013) and others point to the many studies that have reported functional benefit after clinical trials of thrombolytic treatment. For example, a recent meta-analysis (Wardlaw et al., 2012) of 12 randomized, clinical trials (7012 patients) (Mori et al., 1992; Haley et al., 1993; Yamaguchi et al., 1993; Hacke et al., 1995, 1998, 2008; The NINDS rt-PA Study Group, 1995; Clark et al., 2000; Alberts et al., 2002; Wang et al., 2003; Davis et al., 2008; The IST-3 Collaborative Group, 2012) of intravenous tissue plasminogen activator given within 6 h of symptom onset, reported a significant increase in the proportion of patients who were alive and independent at the end of follow-up (46.3% in treated versus 41.3% in controls). However the uniform improvement in functional status reported in these trials is difficult to reconcile with the lack of clear evidence of increased post-treatment recanalization and needs explanation.

Pointed criticism regarding the interpretation of these clinical trials has been previously made (Hoffman and Cooper, 2003; Hoffman and Schriger, 2009; Fatovich et al., 2012; Newman and Shreves, 2012; Radecki, 2012; Brown et al., 2013) and is not discussed further. Only two issues regarding the reliability of post-stroke functional studies are highlighted here. As has been pointed out previously (Wardlaw et al., 2009) true blinding in clinical trials of tissue plasminogen activator treatment may be
exceedingly difficult because its biological effect on the coagulation system leads to a bleeding tendency (manifest as easy bruising and ecchymoses, prolonged bleeding from venipuncture sites and gingival or conjunctival haemorrhages). To conceal knowledge of this effect in clinical trials of thrombolytic therapy, efforts have been made to ensure that follow-up was carried out by a different physician from the one involved in the acute care of the patient. However, a meta-analysis reveals that this may have been achieved in only 8 of 26 trials (Wardlaw et al., 2009). Secondly, in the main phase of the largest (3035 patients) clinical trial, IST-3, patients were not blinded to the treatment they received (IST-3 Collaborative Group, 2012). Physician, patient or caregiver awareness of tissue plasminogen activator treatment status (even if limited to only some in all of these studies) and consequently an expectation or hope for benefit may have skewed the results unidirectionally towards the modestly positive results reported. This confounding effect was clearly shown in the 18-month follow-up of the IST-3 study, when patients who knew they had received thrombolytic treatment reported significantly better functional outcomes than those who were unaware; by comparison, when not aware of treatment status, treated and control groups reported identical functional outcomes (The IST-3 Collaborative Group, 2013).

Role of endogenous and administered tissue plasminogen activator in clot lysis

In a patient who presents with an acute ischaemic stroke, secondary to a cerebral arterial thrombotic occlusion, the endogenous fibrinolytic system has been unsuccessful in rapidly lysing the developing thrombus and restoring flow. Administering additional tissue plasminogen activator intravenously (up to 4.5 h after the clot has already proven resistant to physiological fibrinolysis) with the hope of now achieving thrombolysis, assumes that the critical cause of the failure of clot lysis is a deficit in tissue plasminogen activator or that thrombolysis can be enhanced by additional exogenous tissue plasminogen activator. However the amount of tissue plasminogen activator available to bind to the fibrin clot may not be a limiting factor in the efficiency of clot lysis in vivo. Normally tissue plasminogen activator circulates at a concentration of 5–10 ng/ml and tissue plasminogen activator is released locally from vascular endothelial cells in the region of the thrombus (Collen and Lijnen, 2005). Rapid and transient local release of tissue plasminogen activator occurs secondary to diverse physiological stimuli including arterial shear stress (Diamond et al., 1989), bradykinin, vasopressin and thrombin in the developing thrombus (Giles et al., 1990; Schrauwen et al., 1995). Local concentrations of endogenous tissue plasminogen activator in the vicinity of the acute thrombus are likely to be already high. In addition, in vitro studies show that unless tissue plasminogen activator is already incorporated into the substance of the clot, when exogenous tissue plasminogen activator is added later, lysis of a preformed clot is inefficient (Brommer, 1984).

These considerations suggest that since clot formation is a balance between the clotting and fibrinolytic system, a large therapeutic surge of exogenous tissue plasminogen activator may prevent the formation of a thrombus (leading to an increased bleeding tendency) but yet have limited or no efficacy in dissolving a pre-existing thrombus. Resistance to thrombolysis is likely to be determined by the structure and permeability of the fibrin clot itself. For example platelet-rich areas in a thrombus which have high levels of plasminogen activator inhibitor-1, PAI-1 (a rapid physiological inhibitor of tissue plasminogen activator) (Zhu et al., 1999) and fibres which are thin and highly branched are known to be more resistant to thrombolysis (Gabriel et al., 1992; Weisel and Litvinov, 2013). Altered fibrin structure associated with resistance to fibrinolysis has been reported in in vitro clots made from plasma of patients with ischaemic stroke and diabetes (Dunn et al., 2006; Rooth et al., 2011). Failure of the endogenous fibrinolytic system to lyse the thrombus responsible for the stroke is likely to be secondary to these factors and it is unclear that this resistance can be overcome by adding even more tissue plasminogen activator.

Balami et al. (2013) state that, although tissue plasminogen activator is effective, several characteristics including location, size, and characteristics of the thrombus may lead to tissue plasminogen activator resistance in some (~50%) patients. However, more worrisome may be the possibility that the occurrence of a stroke, which does not improve quickly, indicates that all such patients are non-responders to endogenous tissue plasminogen activator (and are therefore likely to be non-responders to exogenously administered tissue plasminogen activator). Those who are likely to respond may have already done so spontaneously, secondary to physiological fibrinolysis.

Proposed approach to confirm efficacy of intravenous thrombolysis

Balami et al. (2013) suggest that thrombolysis may even have potential benefit in groups not generally treated, such as wake-up strokes, and strokes in dementia and malignancy patients. However, more pertinent may be the concern that the primary issue of whether intravenous thrombolysis is effective or not remains unsettled.

Regardless of whether one views reports of improvement in functional status following tissue plasminogen activator treatment, as convincing (The NINDS rt-PA Study Group, 1995; Lyden, 2012; Wardlaw et al., 2012; Balami et al., 2013) or not (Hoffman and Schriger, 2009; Fatovich et al., 2012; Newman and Shreves, 2012; Radecki, 2012; Brown et al., 2013) a direct evaluation of the effectiveness of intravenous thrombolysis should be done by performing a pre- and post-treatment (within 24 h), CT angiographic (and if feasible CT perfusion) study to determine unequivocally whether recanalization has been achieved.

However, unlike earlier studies, such a study must incorporate two essential requirements: (i) previous studies have not angiographically studied a sufficient number of untreated patients.
Therefore, performing serial CT angiograms in a sizeable number (for example, ~300) of control ischaemic stroke patients is essential to accurately determine rates of early spontaneous recanalization. Rates of spontaneous recanalization in various subgroups, such as those defined by the location of the occlusion, could also be determined. A claim of successful thrombolysis would require demonstration of early recanalization and reperfusion rates that are significantly higher than that seen due to spontaneous recanalization in the control patients; and (ii) to avoid subjective reading bias and varying interpretations (Wintermark et al., 2013), especially for arteries deemed partially recanalized, it would be important to make all baseline, and follow-up CT angiogram images fully available to all. As digital transmission of high quality radiologic images is now routine, this could be done on a designated website, to allow universal access to all the angiograms and objective review to confirm that recanalization and distal perfusion has indeed been achieved and to what degree and at what frequency. Such clear evidence of increased, early recanalization and restored perfusion (an essential prerequisite for any clinical improvement) would greatly increase confidence in the efficacy of intravenous thrombolytic treatment, and would be likely to lead to increased usage of this treatment (as advocated by Balamí et al., 2013 and the American Heart/Stroke Association).

Conversely, administering intravenous tissue plasminogen activator uses up precious time in the immediate aftermath of an acute ischaemic stroke. If intravenous tissue plasminogen activator treatment is shown to be ineffective, or only effective in a small subgroup, research efforts could be quickly redirected to randomized trials of immediate endovascular therapy with newer retrievable stents (which have been reported to achieve very high recanalization rates from 80–90%) (Brekenfeld et al., 2011; Nogueira et al., 2012; Saver et al., 2012; Broderick et al., 2013) with the hope of improved clinical outcomes.

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