LETTER TO THE EDITOR

Reply: Intravenous thrombolysis for ischaemic strokes: a call for reappraisal

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Sir,

Many thanks for giving us the opportunity to reply to the letter in reference to our review ‘The exact science of stroke thrombolysis and the quiet art of patient selection’ (Balami et al., 2013).

Aside from well documented limitations, recombinant tissue plasminogen activator (rt-PA, alteplase) remains the only evidence-based treatment in acute ischaemic stroke (Balami et al., 2013) with evidence dating back to 1995 for clinical efficacy (NINDS, 1995). In recent meta-analyses containing in excess of 6500 patients, alteplase significantly increases the chance of a favourable stroke outcome if administered within 4.5 h (Wardlaw et al., 2012; Emberson et al., 2014). The most established complication from alteplase treatment is bleeding risk, but there is growing evidence that physicians are more liable to lawsuits for failure to use rt-PA than from complications related to therapy (Liang et al., 2008; Bruce et al., 2011).

We agree with Bhagavati (2015) in that many studies did not carry out assessment of recanalization using the most appropriate methods. This may be down to many reasons including technology and equipment available at the time, purpose of the trial, time, and the protocol carried out. However, the fact remains that rt-PA does improve clinical outcome (Wardlaw et al., 2012; Emberson et al., 2014), independent of whether recanalization is measured or not. Therefore to say that intravenous rt-PA may not be an effective treatment for ischaemic strokes is incorrect, and in fact the recanalization rates with rt-PA—even with accurate angiographic assessment—is higher (21.3% to 57.1%) than spontaneous recanalization (17% to 32%) measured with the same techniques, as stated by Bhagavati (2015). The science of objectively measuring the degree of recanalization does not necessarily correlate with the clinical outcome for the patient. What may be subclinical for one patient could lead to compromise in another. We agree that CT angiography has a high sensitivity and specificity when it comes to assessing recanalization, however, our review did not cover this, nor intend to discuss the differences between methods to assess recanalization.

Bhagavati suggests that some of the failure of recanalization of exogenous rt-PA is because of the failure of endogenous tissue plasminogen activator to lyse the clot. However, we feel that this statement is incorrect. It is well-established that exogenous rt-PA can lead to sustained thrombolysis in vivo in both animal studies (Matsuo et al., 1981) and in humans (Eisenberg et al., 1987). It has also been shown that exogenous rt-PA when incorporated into a pre-existing clot can subsequently lyse that clot (Kimata et al., 1990), suggesting that rt-PA acts to dissolve a pre-existing clot. The fibrinolytic system is a delicate balance between the thrombogenic effects of clot formation and thrombolytic effects of clot breakdown, which if disrupted either way, can lead to...
significant adverse effects. Of course, the formation of thrombi is critical for physiological homeostasis as they prevent bleeding into surrounding tissues. However, at times when unwanted thrombi are formed, such as in stroke and myocardial infarction, the thrombolytic system may not have the sufficient power to overcome the effects of thrombi formation. For example, plasminogen activator inhibitor (PAI)-1 is a potent inhibitor of tissue plasminogen activator and prevents the formation of plasmin, a potent thrombolytic (Keijer et al., 1991). In physiological states, PAI-1 is active in the circulation, allowing clot formation in times of vessel stress. However, in pathological situations such as stroke, overcoming the thrombolytic block of circulating PAI-1 with endogenous tissue plasminogen activator is difficult, hence the need to deliver exogenous rt-PA to overwhelm the inhibitory effects of PAI-1 (Marder, 2011). The advantage with tissue plasminogen activator is that it acts locally by binding to fibrin at the surface of the clot, which activates plasminogen into plasmin, which ultimately thrombolyses the clot (Hoylaerts et al., 1982). So there is ample evidence that tissue plasminogen activator can dissolve pre-existing clots in a localized manner, and that exogenous rt-PA can overcome the inhibitory effects of PAI-1 that endogenous tissue plasminogen activator cannot manage. Yes, the recanalization rates of rt-PA remain variable, and while improving these could be done with newer formulations of thrombolytics that are currently being tested, there remains a substantial clinical improvement with administration of rt-PA not seen with other thrombolytics, despite poor recanalization rates.

The primary outcome measure in our review was clinical efficacy. What is proposed in this letter, having pre- and post-CT angiography measurements, is entirely appropriate for the research setting, but far removed from what is clinically achievable. The manpower required for an instant CT angiography is simply not practicable in all clinical settings. A protocol that necessitated the amount of imaging suggested in this letter would not only be undeliverable but detrimental to patient care primum non nocere. Earlier treatment is associated with better outcome and as we have evidence that rt-PA works, withholding it for further randomized placebo-controlled trials would be highly unethical. The idea of having universal access to angiograms for objective review is in principle possible, but would be practically problematic with data protection issues, obtaining informed consent, and relies above all on compatible imaging software at multiple centres.

Bhagavati (2015) states that for endovascular therapy there are ‘high recanalization rates from 80–90% with the hope of improved clinical outcome’. However, with alteplase we no longer have to rely on hope. There may be an art to patient selection, but the rt-PA trials provide robust scientific evidence demonstrating statistically significant improvement in clinically relevant outcomes.

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References