Letter to the Editor

Ultrasound-Assisted Tissue Plasminogen Activator Delivery to Ischemic Strokes

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The World Health Organization defines stroke as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent cause other than that of vascular origin' (Armstead et al. 2010). Strokes can be broadly classified into two categories: ischemic and hemorrhagic. The former category comprises 80% of all strokes (Armstead et al. 2010; Murray et al. 2010). In adults, ischemic strokes are the third major cause of morbidity and mortality, surpassed only by heart disease and cancer (Armstead et al. 2010; Murray et al. 2010; Frendl et al. 2011). With increasing longevity and a growing proportion of the population over 65yr in North America, death and disability from strokes can be expected to increase (Murray et al. 2010). Current therapies for ischemic strokes, while effective, have significant hemorrhagic risks to the patient and must be administered within a very narrow timeframe (Frendl et al. 2011; Alexandrov 2010). Therefore, there is a need to investigate novel therapeutic agents as well as improve drug administration techniques to acutely decrease the injury caused to the brain in the event of a stroke, while minimizing the potential for hemorrhages and reperfusion injuries.

Ischemic strokes are caused by occlusion of the arteries of the brain, which can be caused by a thrombus *in situ*, or by an emboli, a clot formed elsewhere that migrates to the brain (Armstead et al. 2010). Within the brain vasculature, blood clots form when activated platelets aggregate and inactive fibrinogen forms a fibrin meshwork, thus blocking blood flow and depriving neurons of oxygen and nutrients. Therefore, the current standard for treatment in strokes is thrombolysis, in which thrombolytic agents dissolve the occluding fibrin meshwork that causes the clot (Armstead et al. 2010; Frendl et al. 2011). Currently, the only Food and Drug Administration (FDA) approved thrombolytic agent for acute stroke is the tissue plasminogen activator (tPA) alteplase (Frendl et al. 2011). Fibrinolysis occurs when tPA cleaves the zymogen plasminogen to produce the active serine protease plasmin, which degrades the clot (Armstead et al. 2010). When administered intravenously, tPA has been shown to be more specific to fibrin at the site of adherence than other thrombolytic agents, and can thus degrade the fibrin clot more efficiently (Murray et al. 2010). For this reason, it is the agent of choice in an emergency thrombolytic setting.

Despite its efficacy in an acute setting, there are several conditions associated with tPA use. The administration of tPA within 3 h of the onset of a stroke is associated with an increased proportion of patients with a positive outcome (such as improvement in neurological function) as well as a decrease in the proportion of patients suffering from permanent disabilities (Armstead et al. 2010; Frendl et al. 2011; Daffertshofer et al. 2004; Doomernik et al. 2011). A few reports also suggest that intravenous tPA administration in the 3-4.5 h window confers benefit, albeit with reduced efficiency (approximately 50% in comparison to < 3 h group) (Frendl et al. 2011; Saver et al. 2009). However, it is not always possible to administer this agent within such a narrow timeframe (<4.5 h) since patients often do not recognize the symptoms of a stroke, and may not seek medical attention immediately. As well, administration of tPA can significantly increase the risk of reperfusion injury and intracranial hemorrhage (Armstead et al. 2010; Murray et al. 2010). Although the narrow timeframe for tPA administration remains a challenge, the risk of reperfusion injury and intracranial hemorrhage can potentially be reduced by lowering the dose of tPA administered, while simultaneously improving its efficacy. Currently, investigators are exploring the use of combination therapies that improve the efficacy of tPA as a therapeutic agent, without increasing the dose administered. Specifically, the application of existing biomedical technologies, such as ultrasound, in combination with tPA are currently being investigated to improve patient outcomes.

Sonothrombolysis is one such technique that uses ultrasound waves on the skull to dislodge thrombi from its interface with a vessel. Ultrasound waves deliver momentum to areas of stagnant blood flow, causing agitation and degradation of the thrombus. This process increases the amount of residual blood flow and augments the delivery and penetration of drugs, such as tPA, into the clot and results in a larger area of thrombolysis (Alexandrov 2010; Daffertshofer et al. 2004). Although sonothrombolysis can be performed non-invasively at any time, experimental evidence suggests that the use of ultrasound waves in combination with

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thrombolytic drugs, such as tPA, accelerates enzymatic fibrinolysis and increases the efficiency of the drug (Daffertshofer et al. 2004). One study has shown that rats treated with low-frequency, pulsed ultrasound combined with intravenously administered tPA have smaller area of infarcts compared to untreated controls as well as rats receiving only the drug (Daffertshofer et al. 2004). Clinical trials have also shown optimistic results of using sonothrombolysis in combination with systemic tPA. For example, a clinical trial (CLOTBUST) by Alexandrov *et al* showed that 49% of patients receiving tPA and transcranial Doppler (ultrasound) achieved sustained complete recanalization at 2 h (as shown by ultrasound or CT or MR angiography), versus 30% of patients receiving tPA only (Alexandrov 2010; Tsivgoulis et al. 2008; Alexandrov et al. 2004a; Alexandrov et al. 2004b). CLOTBUST was the first large-scale multi-center clinical trial that confirmed the ultrasound-enhanced thrombolysis effect using diagnostic (low power) ultrasound equipment. However, the CLOTBUST trial was not powered to evaluate efficacy in improving functional outcomes. A meta-analysis by Tsivgoulis *et al* further supported this finding by showing that complete recanalization was achieved in 37.2% of patients treated with tPA and transcranial Doppler compared with 17.2% of patients receiving only tPA (Tsivgoulis et al. 2010). Complete recanalization has been associated with increased likelihood of functional independence (Tsivgoulis et al. 2010). Moreover, a recent meta-analysis by Doomernik *et al* suggests that sonothrombolysis is relatively safe, with few reports of complications such as hemorrhage and embolization (Doomernik et al. 2011). Therefore, combining tPA with sonothrombolysis may significantly increase the efficacy of tPA, and have a positive biological effect.

Considering the enormous familial, societal and financial burden faced by those affected by strokes, there is a need to investigate more efficacious methods that can be used in combination with current therapies for strokes. The rigid criteria for tPA administration as well as the critical 3 h drug administration timeframe greatly limits the number of patients that may receive this treatment. We believe that the most promising option appears to be the augmentation of tPA use with procedures such as sonothrombolysis. Results of animal studies and clinical trials have shown favourable results in terms of efficacy and safety, and the low cost and ease of using ultrasound treatment make it feasible for routine use in hospitals (Alexandrov 2010; Daffertshofer et al. 2004). We believe that sonothrombolysis may supplement tPA infusion in patients to reduce long-term morbidity and mortality. Considering the extended length of time it takes to license a new drug approved by the FDA, this trend towards the combination of biomedical technologies with existing FDA-approved drugs might allow for significant improvements in the efficacy of drug treatments for a wide variety of diseases. Thus, combination therapies could not only serve to reduce the burden on the healthcare system, but also promote and accelerate the integration of biomedical technologies in mainstream medicine.

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