The future of stroke is small

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“The use of nanoparticle based imaging techniques to identify the stroke lesion (i.e., thrombus site or hemorrhagic rupture point) and then simultaneously deliver targeted thrombolytic or hemostatic therapy, offers an exciting new treatment paradigm.”

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There has been a reinvigoration in the field of ischemic stroke over the past couple of years. Several positive trials [1] were published in 2015, demonstrating the superior effectiveness of mechanical thrombectomy in combination with intravenous thrombolysis compared with intravenous thrombolysis alone. The treatment effect in some trials [2] was truly impressive, with up to a 50% absolute benefit in one study of highly selected patients. Concurrently, a new field of prehospital stroke assessment, treatment and research has evolved. Both these developments have given some optimism to the field of neuroprotection, which had previously stalled in the wake of consistently neutral or negative trial results. The prospect of commencing therapy earlier, and getting better access of neuroprotective agents into ischemic brain tissue by the superior recanalization achieved by thrombectomy, raises the possibility that agents previously shown to be ineffective, could possibly have some benefit in this new paradigm of therapy.

Despite this good news, there remain enormous difficulties with applying effective therapies to most stroke patients around the world. Currently, there is a

focus on the organization of systems of care [3], with experts from countries with access to advanced emergency medical transport and interventional neuro-radiology attempting to integrate the most efficient means of identifying and rapidly delivering patients to stroke centers capable of performing mechanical thrombectomy. The logistical challenges are substantial. Mechanical thrombectomy is currently a procedure that only a small number of highly trained practitioners can perform [4]. It is highly labor intensive, requiring a team of technical, nursing and anesthetic staff as well as advanced facilities. Even though data suggest it is cost effective [5], especially when considering the potential for savings because of reduced disability and dependency from stroke, there are substantial establishment costs. I predict that mechanical thrombectomy will remain accessible to only a minority of stroke patients who are fortunate enough to live selected wealthy areas of the world. Even in these settings, a continued problem will be the time delays to recanalization that will remain inherent in the process, limiting the benefit.

KEYWORDS

- nanomedicine • neuroprotection
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- thrombolysis

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There has to be a better way to make stroke therapy more accessible to a greater number of patients, in more countries. One potential strategy, described by Xie, Lee and Chen in 2010 [6], is theranostic nanomedicine; this is the concept of combining diagnostic and therapeutic properties in a single agent utilizing nanoparticle technology. The use of nanoparticle based imaging techniques to identify the stroke lesion (i.e., thrombus site or hemorrhagic rupture point) and then simultaneously deliver targeted thrombolytic or hemostatic therapy, offers an exciting new treatment paradigm. This accurate delivery of drug to the site of the pathology may maximize its action and minimize systemic distribution of the pharmacological agent, potentially reducing side effects. It is possible that this strategy could be based around noninvasive, portable technology such as transcranial doppler ultrasound that could be commenced by paramedics in the prehospital setting. More advanced treatments, possibly relying on MRI could be completed upon hospital arrival.

Recently published work by Wang *et al.* [7], describes the use of thrombus-targeted microbubbles in a mouse model of carotid thrombosis. Their work was based on the development of an antibody against the glycoprotein IIb/IIIa complex, which was combined with a fibrinolytic drug and an echo-enhancing microbubble. This combination resulted in the ability to identify the *in vivo* localized site of thrombosis, deliver therapy and to monitor the progress of the thrombolytic treatment in real time. Simply delivering the drug to the site of the thrombus may not be sufficient to ensure effective thrombolysis. Hemodynamic stasis immediately proximal to the thrombus may limit penetration of drug into the target site. This may explain the frustratingly low rates of recanalization observed with standard intravenous thrombolysis, particularly with large thrombus burden [8]. An *in vitro* model utilizing magnetically activated nanomotors achieved enhanced penetration of tPA into clot interface [9]. A small in human pilot study [10] has taken this further, using tPA tagged to ferromagnetic nanoparticles, drawn into the thrombus site by utilizing a weak magnetic field applied over the skull, from a direction opposite the injection site. Reasonably impressive recanalization was demonstrated, but some problems with systemic hypotension were encountered that will need consideration if future trials are undertaken.

Perhaps the ultimate noninvasive treatment for ischemic stroke could comprise of an

MRI-based system where the vascular occlusion is identified using a contrast agent similar to that described above, combined with a thrombolytic agent, that is activated sterotactically by the MRI magnetic field; ‘nano-magnetic thrombolysis’. MR sequences could be designated as diagnostic, then therapeutic.

Moving such an idea forward poses not only technical and logistical challenges, but possibly some ethical issues as well. Given the success of the combination of thrombolysis together with mechanical thrombectomy it might be very difficult to perform a clinical trial of a new technology at sites where mechanical thrombectomy is readily available. Investigators and subjects might be hesitant to randomize a subject not to receive thrombectomy. Perhaps such trials may need to be conducted in sites without ready access to interventional radiology services and where geographical isolation makes a ‘drip and ship’ strategy difficult, but have sufficient infrastructure, wealth and stroke experience. Australia, Canada, some larger US states and possibly Alpine European regions might be potential regions where such trials could be conducted.

The theranostic approach could potentially be applied to intracerebral hemorrhage (ICH). ICH remains a devastating condition with high mortality and no greatly effective treatment. An individual patient meta-analysis [11] suggested some possible benefit for surgery, and ongoing trials of minimally invasive surgery [12] show some promise, but this approach requires access to an expensive and limited resource; neurosurgeons. Acute blood pressure lowering [13] and early application of neuroprotective agents are reasonable strategies, but only ever likely to be of modest benefit. Hemostatic therapy showed initial promise, notably reducing hematoma expansion, but the FAST trial [14] did not show clinical benefit, with systemic thrombotic complications being problematic. More selective trials [15] utilizing the ‘spot sign’ as a radiological marker of ongoing hemorrhage are underway. The logic of this is to select subjects who might benefit from systemic hemostatic therapy by reducing hematoma expansion, without exposing subjects where expansion has likely ceased already, thereby reducing the potential for thrombotic complications.

A review in this journal in 2011 [16] suggested that new and novel approaches to the treatment of ICH will be required if substantial advances in the management and outcomes of ICH are to be

made. The imaging advances enabling identification of the site of rupture of the small deep penetrating vessels due to lipohyalinosis that underlies typical hypertensive deep ICH were described. It was suggested that intentional selective occlusion of the origin of the lenticulostriate vessels from the middle cerebral artery trunk, using advanced microcatheters might be an approach to minimize hematoma expansion. Unfortunately, all the logistical and access issues pertaining to mechanical thrombectomy would again apply. A theranostic approach to selectively deliver a hemostatic agent such as factor VII to the site of vessel rupture might ensure delivery of the therapeutic agent to the site of the bleeding and minimize the systemic thrombotic complications. Following the approach described above for selective delivery of a thrombolytic agent, imaging, pharmacological, immunological and electromagnetic techniques could be harnessed to deliver the hemostatic drug precisely to the target.

Theranostic-based nanotherapies might therefore offer a way to advance acute treatment for both ischemic and hemorrhagic stroke. The currently evolving models of systems of care incorporating prehospital assessment, treatment and triage [17,18] to appropriate stroke centers could incorporate theranostic techniques in a step-wise fashion. In many systems there may be an opportunity to commence a cocktail of neuroprotective agents in the prehospital setting, with a view to slowing the ischemic cascade or reducing toxic effects of hematoma expansion. The preceding discussion has focused on theranostic nanotherapy in terms of aiding thrombolytic or hemostatic drug delivery. It might be possible to also consider applications to neuroprotective agents, possibly by considering molecular targets of neural tissue injury that are common to both ischemic and hemorrhagic stroke, potentially using an immunological approach. This paradigm would be important in the prehospital setting prior to the neuroimaging, when the stroke subtype (ischemic vs hemorrhagic) is yet to be determined.

Once imaging has been performed, identifying the stroke subtype, then specific therapies, either thrombolytic or hemostatic could be commenced; again these might involve the immune targets. In some settings this step could occur in the prehospital phase, if portable imaging is available. This might include portable ultrasound devices that could initiate focused therapy administration. The next step is the more precise identification of the vascular lesion, either thrombosis or vascular rupture. Until further technological advances are made with portable imaging, this is likely to be available only at high level hospitals where 'nanomagnetic thrombolysis or hemostasis' could be administered.

The future of stroke therapies must not be slowed by a perception that recent successes with mechanical thrombectomy indicate that there is now an ideal treatment. It is unlikely that this treatment technique will ever reach the majority of stroke patients, and furthermore, hemorrhagic stroke remains in desperate need of an effective therapy. Novel, and 'big picture' thinking will need to include systems management, transportation and imaging technologies. The new concept of theranostics will provide an opportunity to combine advances in imaging technology and immune and nano-technology-aided pharmacotherapeutics. So in order to pursue these 'big picture' advances in stroke treatment, we will have to 'think small'!

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