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Viewpoint Article

Non-invasive thrombectomy: magnetized antibodies in reperfusion of thromboses

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Abstract

Background: Five multi-center randomized controlled trials have shown superior outcomes for mechanical thrombectomy to standard intravenous thrombolysis for acute anterior ischaemic stroke. This idea-paper aims to provoke multi-disciplinary expertise to develop a less invasive and more rapid thrombectomy technology. The hypothesis is that by adapting existing technology to magnetize in vivo blood clots, we should be able to dislodge clots from major vessels magnetically and achieve minimally invasive reperfusion.

Methods: First, magnetized antibodies against specific epitopes in blood clots must be developed (such as the previously used Fibrin Beta-chain specific antibody, 59D8) and an external portable magnetic device with superlens magnetic-field focusing would be used to dislodge and guide the clot proximally to establish reperfusion; subsequently, the clot will be removed. A distal magnet, statically held at the original location of the dislodged clot, would prevent microemboli from occluding distal vessels during dislodgement and removal of the clot.

Conclusion: Developing specific antibodies against in vivo blood clots (immunology) with attached superparamagnetic nanoparticles (nanoscience) and an external portable magnetic device with a focused magnetic flux (applied medical physics) will significantly improve time to revascularization in acute ischaemic stroke, minimize risks of intervention, and thus improve outcomes further.

Keywords: Stroke, Thrombosis, Thrombectomy, Clot Retrieval, Magnetized Antibodies, Portable Magnetic Device

Background

Ischaemic stroke is a leading cause of mortality and morbidity in the world, and constitute 85.0% of all strokes, costing the UK National Health Service (NHS) over £3billion a year [1]. In vivo, acute blood clots may be visualized on Computed-Tomography (CT) scans as hyperdense and radio-opaque to X-rays. Intrinsically, the blood clot has chemically altered blood components which arise as a result of the coagulation cascade and platelet adhesion and aggregation.

Intravenous or intra-arterial thrombolysis with recombinant tissue-plasminogen activators (e.g., alteplase) have remained the gold-standard hyperacute treatment of ischaemic stroke, and previously were the standard of treatment for ST-elevation myocardial infarctions prior to primary percutaneous coronary intervention.

Several studies have shown a modest benefit of thrombectomy interventions. In meta-analyses and subgroup analysis, invasive neuro-radiologically performed thrombectomies are of most benefit the earlier they are performed and in patients with more severe strokes as quantified on the National Institutes of Health Stroke Scale (NIHSS) scores [2]. Five multi-center, randomized controlled trials have shown mechanical thrombectomy devices to be superior (outcomes on the modified Rankin Scale at 90 days) to standard treatment with intravenous thrombolysis alone (in anterior circulation ischemic stroke caused by a proximal large artery occlusion) [3-7].

The procedures themselves carry risk and benefit is limited due to dependence on expertise, speed of transfer to a centre capable of vascular intervention as well as time required for the preparations for intervention. Therefore, developing a non-invasive technique that can dislodge and remove clots would improve time to thrombectomy, enhancing benefits, and reduce risks associated with mechanical thrombectomy.

Methods

Overview

What is proposed here is to develop antibodies specifically against an epitope restricted to in vivo blood clots. The Fragment crystallizable (Fc) region of the antibody would be pre-attached to superparamagnetic nanoparticles.

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After intravenous or intra-arterial administration of this magnetized antibody, a non-invasive transcutaneous external magnet would be applied to the region of the clot, for example, for carotid occlusions. The externally applied magnetic field would be varied in order to dislodge the clot from the vessel, with the option of using ultrasound to assist the mechanical dislodging.

A second bolus of magnetized antibody would then be injected to coat the clot further as more epitopes are revealed during dislodgement. The magnetic field can then guide the clot against arterial blood flow towards a more proximal superficial artery, thus establishing reperfusion - while a more distal magnet remains to catch any microemboli dislodged from the clot. An arterial puncture can then be performed to remove the clot entirely (in later iterations, instead of arterial puncture, intra-arterial thrombolysis and/or ultrasound could conceivably be used to break the clot in situ).

1. Antibodies

1a. Super-paramagnetic-nanoparticles (MNP)

These have already been used for magnetized drug delivery. Although high loadings (>100 µg/mL) of MNPs cause cytotoxicity, toxicity studies on magnetic nanoparticles show that these particles can be biocompatible [8].

1b. In vivo blood clot specific epitope (Fibrin)

In studies performed in the late 1980s, Fibrin Beta chain-specific antibody 59 D8 – which provided the highest level of binding to clot – binds fourteen-fold better to blood clots than the control (antidigoxin antibody) [9]. Fibrin would thus be the most likely candidate for a specific epitope. Other blood clot epitopes could be considered if anti-Fibrin antibodies are deemed insufficiently specific for blood clots after testing.

2. Transcutaneous Portable Magnetic Device (TPMD)

Recently the Food and Drug Administration (FDA) in the USA issued a substantial equivalence approval for a portable magnetic resonance imaging scanner (MRI). This low magnetic field scanner can provide images of the brain [10].

A similar bespoke device would be required for this purpose, a portable high-field machine, to be applied via the transcutaneous route after the clot is magnetized.

Alternatively, a device integrated into an MRI scanner to automate the process and localize the clot, akin to radiotherapy preparation.

2a. Magnetic flux focusing and portability

In order to increase the magnetic force on the clot with increased chances of dislodgement and reperfusion, besides an advanced integrated version within MRI-stroke specific scanners, the portable external magnet can utilize the following design concepts:

i) Solenoid: increased magnetic flux within the solenoid. It would be difficult to access the clot from the carotid. Thus, a superlens design is preferable (see below).

ii) By focusing on a magnetic field, the size of the TPMD could be reduced, and a smaller electric power source would be required than would be feasible with the magnetic field of an unfocused magnet [11]. This allows for miniaturization and a portable TPMD, which may be used even in the emergency department itself – thus substantially reducing the preparation time required for mechanical thrombectomy in an angiography suite.

iii) Superlens metamaterials with magnetic permeability of ¬-1 can focus the near fields of magnetic flux and improve efficiency, allowing for a smaller, more portable TPMD [12].

2b. Dynamic Magnetic field to dislodge the clot (prior to the second injection of magnetized Antibody)

There will be a need for mechanical, magnetic, ultrasonic, or combined mechanisms to help dislodge the clot. This may be achieved by:

i) altering the strength of the TPMD magnetic-field focused on the magnetized clot

ii) moving the portable external magnet to alter the distance between it and the magnetized clot. This can be an automated mechanical process occurring in the hand-held device. While the portable device is held constant, the external magnet within it moves.

iii) An electrically controlled alternating magnetic field, similar to that used in MRI. These field-altering methods may not be sufficient to dislodge the clot. A mechanical or ultrasonic component may be required.

3. Magnetic Microemboli Filter (MMF)

The MMF would be a straightforward permanent magnet which occupies the original location of the clot. After the TPMD has dislodged the clot and is guiding it proximally, the MMF would prevent arterial blood flow from throwing microemboli off the retrieved clot more distally. The MMF would magnetically prevent distal micro-embolization during dislodgement and removal of the clot by the TPMD.

Discussion

The key to better outcomes in strokes is rapid thrombectomy or thrombolysis, with the former showing improved outcomes, especially when clots are retrieved without delay. Within a few minutes of hypoxia or lack of blood flow, nervous tissue begins to die.

Current thrombectomy procedures puncture the skin and artery, whether in the leg (femoral) or arm (radial), and a clot retrieval device is advanced up towards the heart and then into the blocked artery. Risks include pulmonary embolism, embolic strokes, infection, and damage to the blood vessel at the site of the clot. The combined methodology outlined above has the potential to not only expedite interventions but also minimize risks due to no clot retrieval device being advanced into the arterial system. This is achieved by a hand-held TPMD that can be used immediately after magnetized antibody injection, reducing the duration of the ischaemic brain.

Further work based on the specifics of the antibody and TPMD capability will be required in the form of a theoretical calculation of required magnetic field strength of the TPMD using fluid mechanics. It will be necessary and may be possible, using the data below, to determine the theoretically required TPMD field-strength in order to magnetically hold on to the clot and steer it against blood flow:

i) Antibody specificity to blood clots.

ii) MNP strength.

iii) Arterial blood flow dynamics, e.g., in carotid arteries

iv) Vessel and blood clot distance from the external magnetic device (ultrasound estimation of soft tissue thickness between skin and vessel).

Furthermore, a calculation is required using the above data to ensure there are no major shearing forces on other organs (e.g., endothelial cells of intact patent vessels) to minimize side effects from less specifically bound MNP around the body. For example, using Fibrin beta-chain specific antibodies, we would need to ensure that these are sufficiently specific to prevent significant binding of the magnetized antibodies to other tissues.

Conclusion

The outlined innovative method has the potential to improve ischaemic and embolic stroke outcomes.

Abbreviations

NHS: National Health Service; CT: Computed-Tomography; NIHSS: National Institutes of Health Stroke Scale; Fc: Fragment crystallizable MNP: Magnetic Nanoparticles; FDA: Food and Drug Administration; MRI: Magnetic Resonance Image; TPMD: Transcutaneous Portable Magnetic Device; MMF: Magnetic Microemboli Filter

Declarations

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Availability of data and materials

Data will be available by emailing a.alim-marvasti@ucl.ac.uk

Authors' contributions

Ali Alim-Marvasti (AA-M) is the principal investigator of this manuscript (Viewpoint). AA-M is responsible for the study concept, design, writing, reviewing, editing, and approving the manuscript in its final form. AA-M read and approved the final manuscript.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki; however, Viewpoint Article need no ethic committee approval.

Consent for publication

Not applicable

Competing interest

The author declare that he has no competing interests.

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