DEBATE: ARE NEUROPROTECTION AGENTS STILL AN OPTION FOR ACUTE ISCHEMIC STROKE (AIS)?
NO
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Ischemic stroke remains a leading cause of morbidity and death for which few therapeutic options are available.

The development of neuroprotective agents, a once promising field of investigation, has failed to translate from bench to bedside successfully.

A huge number of pharmacological agents targeted at neurotransmitter receptors and ion channels have been shown to reduce ischemic brain damage in animal models. Many neuroprotective drugs have been tested in more than 100 clinical trials (http://www.strokecenter.org/trials/), but no clear evidence of clinical improvement with any neuroprotective drug has yet been obtained in clinical trials in stroke patients. Among the failures are trials with aptiganel, selfotel, clomethiazole, eliprodil, D-CPPene, lubeluzole, gavestinel, and BMS 204352 that were suspended before completion of patient recruitment or failed to provide compelling evidence of clinical efficacy. Some trials were discontinued due to neurotoxicity. NXY-059 showed significant neuroprotective properties in the SAINT-I phase III clinical trial, but failed in the second phase III trial (SAINT-II trial).

The discrepancy in results regarding neuroprotective agents in animal experiments compared to clinical trials was a major problem. There are many factors (model selection, anesthetic choice, physiological monitoring, model success criteria, embolus property, reperfusion damage, infarction area, therapeutic time window, drug penetration, blood concentration, gender difference, and outcome evaluation) responsible for this phenomenon. In particular, the failure to predict acute neuroprotective drug efficacy from preclinical data has led to the relevance of animal stroke models being questioned.

Inadequate evaluation of animal experimental studies before proceeding to clinical trials and disparity in the results of safety and efficacy in animal experiments and clinical use widely discussed. Quality assurance criteria for preclinical stroke research published by the Stroke Treatment Academic and Industry Round (STAIR) table and Stem Cell Therapy as an Emerging Paradigm in Stroke (STEPS) committees addressed the pitfalls and problems in common preclinical study designs that may lead to false-positive results.

Problems about **transport of small-molecule drugs across the BBB** to the site of action should be specially mentioned. Drugs that cross the BBB in small animals when it is disrupted under experimental conditions may not do so in human patients with intact BBB.

The last 30 years have seen significant progress in our understanding of the pathophysiology of ischaemic stroke and the understanding of mechanisms that contribute to tissue damage. The ischaemic cascade, starting with a severe focal
reduction in cerebral blood flow and culminating in cell death and infarction, has many intervening and interlinking steps that have provided a number of potential drug targets. However**, the adequate target(s) for neuroprotection should still be better identified**.

In previous trials drug targets included neurotransmitter receptors and ion channels, free radicals, cytokines and inflammatory mediators, enzymes and membranes. However, the important role should be not simply to protect the neurone but rather the neurovascular unit: the neurone plus the supporting glial and vascular cells within its immediate environment, which includes astrocytes, pericytes, microglia, oligodendrocytes and the endothelial cells of microvessels. Understanding of the complex response of the neurovascular unit to ischemic injury is still incomplete, thus demanding additional research.

Failure of drugs such as NMDA antagonists to protect cerebral white matter from ischemic damage may have contributed to lack of functional improvement in clinical trials of these agents.

Cellular and molecular pathways underlying ischemic neurotoxicity are multifaceted and complex. Although many potentially neuroprotective agents have been investigated, the simplicity of their protective mechanisms has often resulted in insufficient clinical utility. Human stroke is a highly heterogeneous condition, and treatment targeted at a single mechanism in the ischaemic cascade is unlikely to be universally effective.

Combination therapy or single drugs with multiple targets and actions are more likely to be effective. There is need for a neuroprotective agent with multiple modes of action.

Still, there are promising therapeutic avenues. Emerging evidence indicates an increasing role of neuro-immune crosstalk and neurotrophic methodologies. Cell/gene based approaches are an emerging paradigm in stroke research. Activation of the endogenous protective mechanisms could be a more promising strategy for the development of new therapies against stroke and neurodegenerative disorders. Hypothermia following cerebral ischemia delays the onset of ischemic histopathological alterations.

A possible reason for lack of translation was **inappropriate patient selection**, the failure to acknowledge the greatest risk factor for stroke, age, and other common comorbidities such as hypertension, obesity, and diabetes that are associated with stroke, as well as difficulties in evaluating results in a heterogeneous group **of stroke patients**.

Penumbra is a key therapeutic target for acute stroke therapies. Some clinical trials were compromised by the **lack of penumbra imaging**, patients being recruited on the basis of time from stroke onset, rather than detection of potentially salvageable tissue.

A major cause of failure could be the lack of **efficacy and safety issues**. Definition of the effective dose in clinical trials has been a recurring issue in anti-ischemic drug development because of concerns about adverse effects. Many small-molecule neuroprotectives have poor safety profiles

The translation of neuroprotective agents for ischemic stroke from bench-to-bedside has largely failed to produce improved treatments. Despite decades of thorough research, immediate thrombolysis using recombinant tissue plasminogen activator is currently the only approved therapy for ischemic stroke.

Neuroprotection agents still are NOT an option for acute ischemic stroke and is unlikely that any neuroprotective drug would be successful in a large and expensive clinical trial, <u>unless</u>:

- knowledge is learnt from the large number of clinical trials for neuroprotectants against stroke that yielded mostly disappointing outcomes
- the preclinical evaluation is rigorous and detailed
- patients selection is well-planned and can be aided by brain imaging and genotyping
- trials are focused to determine if neuroprotectives can extend the therapeutic window and reduce reperfusion injury: combination therapy with tPA and a neuroprotective agent represents the next step forward from single agent studies in acute ischemic stroke.

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