Martin Denis

Feeding after stroke

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Many patients admitted to hospital with an acute stroke are under nourished. Many have swallowing problems and this, with other post stroke impairments, contributes to worsening of nutritional status in a significant minority. Poor nutrition is associated with worse survival and functional outcomes. Policies for identifying under-nutrition, swallowing difficulties and feeding patients can contribute to improving patient outcomes. Prof Martin Dennis will discuss these issues, focusing particularly on the evidence from large randomized controlled trials.

Nils Wahlgren

Safe Implementation of thrombolysis in stroke – European perspective

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SITS (Safe Implementation of Treatments in Stroke) is a unique collaboration involving about 700 clinical centres in 35 countries. The aim of the SITS collaboration is to support implementation and quality development of evidence based stroke treatments, to serve as a general stroke register and to perform clinical trials and other research studies in stroke.

SITS was commissioned by the European Union Commission to monitor implementation into clinical routine of intravenous thrombolysis within the setting of the SITS Monitoring study (SITS-MOST) and by the European Union Public Heath Executive Authority (PHEA) to support evidence based stroke treatments in new EU member countries within the SITS-EAST project. Moreover, SITS will form the clinical trial platform within the new EUSTROKE consortium, which received the 'Combatting stroke' research grant within the European Union Research Framework 7.

The SITS-EAST project is now in its initiation phase, during which guidelines will be agreed upon, centres will be classified according the level of stroke services and new centres will be recruited. The next phase will include how to work with the guidelines and establish evaluation criteria.

The establishment of intravenous thrombolysis and other evidence based stroke treatments is now in fast development and this implies an obvious need for quality development and benchmarking. The SITS EAST project may become the leading instrument for this process in Europe.

Title

SITS-ISTR ('Safe Implementation of Thrombolysis in Stroke' (SITS)-International Stroke Thrombolysis Register' (ISTR), is a prospective, international, internet-based monitoring registry for safe implementation of thrombolysis in acute stroke. A pilot version of SITS-ISTR was launched on 1 January 2001, the actual version was launched on 1 January 2003.

Background and purpose

SITS was initiated by a group of ECASS investigators following the publications of the NINDS1 and ECASS trials2. The aims were to facilitate safe and broad implementation of thrombolysis and to amplify the benefit, e.g., by shortening stroke onset to treatment time, an important prognostic factor. There was concern that safety and efficacy of the treatment might differ between RCTs and the real-life situation, during implementation into clinical routine. This could occur if treatment criteria were less strictly followed and the treatment was new to many centres. A professional network involving experienced investigators could support rt-PA implementation by educational initiatives and by providing an interactive database over a secure internet connection, the SITS-ISTR. Daily updated local statistical reports benchmarked to national and international outcomes were considered important feed-back.

The main purposes of SITS-ISTR are:

1. To support the process of broad implementation of thrombolysis in stroke so that the treatment may reach all patients who may benefit.

2. To support amplification of the treatment effect, e.g., by shortening of onset to treatment time.

SITS-MOST

Title

SITS-MOST (MOnitoring Study) is an open, prospective, multicenter, observational, safety monitoring study for all 15 European Union (EU) member states as of 2002, plus Norway and Iceland. Centres within these countries were asked to participate provided that they meet protocol-specified quality criteria. Recruitment of patients in SITS-MOST started in January 2003 and originally required to continue to the end of 2005. The European Medicines Evaluation Agency (EMEA) has recommended closing the SITS-MOST study, since they consider that the main objectives of this study have been achieved. Recruitment patients in SITS-MOST stopped treated after 30 April 2006. Follow up will continue until 30 September 2006. The SITS-MOST cohort is embedded within SITS-ISTR.

SITS-ISTR (International Stroke Register) is now expanding its activities, while the SITS-MOST (Monitoring Study) is completed. SITS-MOST was a defined part of SITS-ISTR and all further recruitment now continues solely in SITS-ISTR. So continue to register patients as usual!

SITS is now launching three new activities that will further increase the value of participation in SITS and lead to improved management of stroke. Of these, SITS 2009 @ 5% includes European Union and EMEA affiliated countries. A further initiative involving non-European Union countries will be announced shortly.

– SITS 2009 @ 5%: Members of the SITS Network strongly believe that more patients could be treated with thrombolysis. The purpose of the new project SITS 2009 @ 5% is to reach at least the level of 5% treated with thrombolysis of all stroke patients in each centre and each country within three years. For countries already at this target a higher objective will be set – SITS 2009 @ 5% plus.

– Introduction of new treatments in stroke: If successful in the THRUST study, thrombectomy in stroke will be a new treatment added to the "SITS Portfolio" in addition to thrombolysis. More new treatments will follow in due course - we are closely following the outcome of other stroke treatments, for example haemorrhage treatment and neuroprotective drugs.

– Keeping track o¬n all your patients: Some countries have national stroke registers, others have not. For those without a stroke register, SITS will provide an opportunity to document also your patients not receiving thrombolysis. It provides an opportunity to compare demographic and baseline data, time logistics and outcome between patients treated and not treated with thrombolysis

THRUST

The THRUST (Thrombectomy in Unsuccessful Stroke Thrombolysis) study

What is the clinical background for the study?

About o¬ne third of all patients treated with intravenous thrombolysis within three hours after o¬nset of stroke have not improved 2 hours after start of treatment. The prognosis of this group of patients is poor in comparison to those with some degree of improvement at that stage. Thrombectomy may offer substantial benefit for these individuals and considerably enhance the overall effect of reperfusion interventions.

Which intervention will be studied? THRUST will compare the effect of thrombectomy using the Merci Retriever versus no intervention following unsuccessful intravenous thrombolysis, defined as lack of improvement o¬n the NIH neurological scale after two hours compared with the results immediately before start of treatment. CT angiography must confirm a retrievable occlusion. Centres will be invited for participation in THRUST based o¬n experience from Merci in clinical routine, such as thrombectomy in later time windows, direct intervention in basilar artery occlusion or even in selected cases of unsuccessful i.v. thrombolysis. Free training will be provided o¬n a first-come basis.

Why is this important?

Intravenous thrombolysis is the first evidence based pharmacological treatment for acute stroke. This treatment provides a highly significant benefit to patients who would otherwise remain dependent o¬n others for daily living activities. The effect of i.v. thrombolysis is frequently experienced during the o¬ne-hour infusion of rt-PA or soon thereafter, following recanalization of the occluded vessel. In about o¬ne third of the patients, however, no improvement is seen at the two hours control. An additional intervention at this stage, such as thrombectomy, may be required to achieve recanalization.

Why Merci?

The Merci Retriever was cleared by the United Stated Federal Drug Agency (FDA) in 2004, based upon the safety and efficacy data gathered during the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial. The Retriever also has the European Union's CE mark approval.

The results of the MERCI trial were published in Stroke in July of 2005 (Smith WS et al, Safety and Efficacy of Mechanical Embolectomy in Acute Ischemic Stroke: Results of the MERCI trial. Stroke 2005, 36:1432-1438). More recently, interim results from the o¬ngoing Multi MERCI trial (presented at the International Stroke Conference,

Kissimmee, Florida, February 2006) suggest that the Merci procedure is also safe and effective in failed thrombolysis patients. The Merci procedure is currently being performed in over 150 centres in the US. It is estimated that over 3,000 patients have been treated with the device to date.

DANIEL BERECZKI

Evidence based thrombolysis

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Evidence Based Medicine is a method of decision making when we decide which option is the best for a given patient in a given situation by considering the most reliable scientific evidence from clinical research. The level of scientific evidence depends on the amount and the quality of research data regarding the intervention in question. Systematic reviews of randomized controlled trials give the strongest scientific evidence.

Atherothrombotic disease may affect several organs, like the brain, the heart and the lower extremities causing ischemic stroke, myocardial infarction or gangrena of the extremities. To dissolve the occluding clot, i.e. thrombolysis may save the ischemic tissue from permanent damage, therefore seems to be a promising approach to treat atherothrombotic diseases. Thrombolysis may have other indications like pulmonary embolism, deep vein thrombosis of the extremities and there are some possible neurological applications like acute ischemic stroke, intraventricular hemorrhage, intracerebral hemorrhage and cerebral sinus/deep vein thrombosis.

Based on Cochrane reviews, thrombolysis may be beneficial in deep vein thrombosis of the lower extremities, but the optimal drug, dose and route of administration has to be determined in future trials. There is not enough evidence to decide if surgery or thrombolysis is better to treat acute limb ischemia. A meta-analysis of randomized controlled trials did not find enough evidence to decide if thrombolysis or heparin treatment is better for patients with pulmonary embolism.

Of the possible applications in central nervous system (CNS) disorders, there is no available evidence from randomized trials regarding the efficacy and safety of thrombolytic therapy in dural sinus thrombosis. There are only cohort studies describing rtPA or urokinase use in intraventricular or deep cerebral hemorrhages. Most trials in CNS disorders were performed in ischemic stroke and the Cochrane review of Wardlaw et al (2003) gives the best overview: thrombolytic treatment resulted in significant net reduction in death and disability, in an increase in death, and an increase in hemorrhagic complications. The outcome seemed better with earlier application and if rtPA was the thrombolytic agent.

rtPA has been licensed for intravenous use in patients within 3 hours of stroke onset. The currently ongoing IST-3 trial will help to decide several unsettled issues, like the possible expansion of the 3-hour time window, inclusion of people over 80 years of age, and those with mild and severe stroke signs.

PETER SANDERCOCK

Use of thrombolysis outside the 'classical' indication: should we or shouldn't we?

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It is now 12 years since the publication of the modest-sized 624-patient National Institute of Neurological Disorders and Stroke (NINDS) trial of iv rt-PA, that led to the FDA approval in 1996 of thrombolysis. As thrombolytic therapy is one of the very few effective treatments for acute stroke, wider implementation would be desirable. Yet, there is a major mismatch between expert opinion and guidelines (which support thrombolysis for selected patients within 3 hours of onset) and clinical practice. rt-PA for stroke has not been widely implemented in clinical practice; large-scale surveys suggest only 1-2% of stroke patients in developed countries receive it. Two factors are responsible in part for the poor implementation: the paucity of data on the effects of rt-PA treatment in many categories of stroke patients, especially the elderly and those who present more than 3 hours after onset; and the continuing debate over the evidence under-pinning licensed use (e.g. Australian Emergency Medicine physicians have refused to endorse the current Australian Governmental approval for rt-PA treatment for stroke because of ongoing debate over the trial data). Unless additional trial evidence establishes benefit for a wider variety of patients outside the current licence, especially among the elderly, the implementation – and public health impact - of this treatment will remain very limited.