PRESS RELEASE

ESOC 2021 Daily Highlights: What's the latest in hyperacute stroke treatments?

On the first day of ESOC 2021, we heard from researchers and their ongoing effort to look for early treatments to improve people who have suffered a bleed in their brain. We also learnt about the evidence of neurosurgery for cerebral venous thrombosis, a rare type of stroke. Studies of several early treatments for acute ischemic stroke were also presented.

TRAIGE trial

When given to selected patients who have acute intracerebral haemorrhage (ICH) with signs of expansion on brain imaging, is tranexamic acid effective at reducing ICH growth, death and disability?

Almost 40% of patients with ICH die within the first month and only about a third go on to live independently after an ICH. There is a lack of effective treatment for patients with ICH. Expansion of ICH on brain imaging is a predictor of poor outcome. A treatment known as Tranexamic acid has previously been shown to reduce ICH expansion, but this did not translate into clinical benefit.

The TRAIGE trial, a multi-centred randomised controlled trial in China, investigated the effectiveness of tranexamic acid, compared to placebo in a selected group of patients who had high-risk imaging features indicating ICH expansion (the spot, black hole or blend sign). 171 participants were randomly allocated to tranexamic acid or placebo within 8 hours of symptom onset. There was no significant between-group difference in the primary outcome—ICH growth (defined as >33% relative growth or growth by 6mls) within 24hours of intervention. Absolute decrease in ICH volume and disability outcome did not differ between groups. Death at 90 days occurred in 8% in the tranexamic acid group, compared to 10% in the placebo group but this was not statistically significant.

Subgroup analysis suggests a trend towards less hematoma growth when tranexamic acid was given within 4.5 hours, consistent with the trend shown by TICH-2 and STOP-AUST trials.

Dr Liu, Co-PI of the TRAIGE trial added, "Further patient selection, earlier intervention and large clinical trials are needed to assess the safety and efficacy of tranexamic acid in ICH patients".

TRAIGE trial has been published in Stroke and Vascular Neurology:
https://svn.bmj.com/content/svnbmj/early/2021/04/01/svn-2021-000942.full.pdf

ANNEXA4 Study

Adexanet Alfa, a reversal agent for blood thinners, may be useful in major bleeding caused by blood thinners such as apixban and rivaroxaban.

Oral anticoagulants, or blood thinners, such as apixaban and rivaroxaban are used to prevent and treat blood clots. Unfortunately, anticoagulation-related major bleeding events are not uncommon even with the new generations of anticoagulation drugs such as factor Xa (FXa) inhibitors (e.g. apixaban, rivaroxaban). Andexanet alfa is an inactive form of FXa that can reverse FXa inhibitors. The drug is recommended by a few recent guidelines for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, but this was based on limited evidence.

In the largest prospective cohort registration study of its type, the ANNEXA-4 study, Milling and colleagues recruited 479 patients with major bleeding whilst taking FXa inhibitors. Over two thirds of the sample were patients who were bleeding in the brain. All patients had the last dose of FXa inhibitor within 18 hours.

They showed that treatment with andexanet alfa successfully reduced anti–FXa activity for all anticoagulants studied. Good or excellent haemostasis (i.e. bleeding was stopped) was achieved in 80% of all patients, independent of age, sex, site of bleeding or andexanet dose.

Clotting (thrombotic) events as an unwanted outcome of reversing the effect of anticoagulation occurred in 50 patients (10%) within 30 days and there were no thrombotic events after restart of oral anticoagulation.

Was there a clinically relevant nadir? The investigators found that for all patients, a nadir of 30ng/ml was associated with lower mortality and for patients younger than 75 years, with some suggestion that lower anti-FXa was associated with a lower mortality. Further studies to evaluate the benefit of andexanet alfa in major bleeding associated with anticoagulation, including intracerebral haemorrhage, are warranted.

DECOMPRESS2 Study-Final Results

Promising findings on decompressive neurosurgery for patients with severe cerebral venous thrombosis

Cerebral venous thrombosis (CVT) is a rare type of stroke. It can be life-threatening when patients develop signs of brain herniation, indicating increased pressure around brain structures responsible for vital functions. Decompressive neurosurgery is recommended in patients with CVT and signs of impending brain herniation but the level of evidence supporting this practice is low. The DECOMPRESS2 study sought to investigate the benefit of decompressive neurosurgery in CVT patients in a large multicenter prospective observational study. Level of disability was measured on the Rankin Scale at discharge, 6 and 12 months after treatment. Patient/caregiver opinion on the benefit of surgery was also recorded.

118 patients from 15 centres in Europe, Asia and America underwent decompressive neurosurgery. The majority of these patients were young (median age 38 years) and over half were women. The majority of the decompressive neurosurgery procedures were performed within 1 day after diagnosis.

Despite having a severe clinical condition at baseline, two thirds of CVT patients were alive and more than one third were independent at one year after decompressive neurosurgery (33.9% patients had died, 35.6% were independent, 10.2% were severely dependent). Decompressive neurosurgery was judged as beneficial by 4 out of 5 patients/caregivers.

'It would probably be considered unethical to randomise patients with this rare type of stroke given that without surgery, these patients are likely to die. Further research should look at how to further reduce the number of deaths in those who have the surgery.' Jose Ferro, the study PI, added.

MR ASAP trial

Could rapidly applied nitroglycerin in the ambulance help to restore the cerebral blood supply in acute stroke and improve clinical outcomes?

Previous evidence suggested that the administration of nitroglycerin improved functional outcomes in patients with acute stroke when applied rapidly. Nitroglycerin is well known in cardiology as a symptomatic therapy for coronary syndromes due to its dilatory and blood pressure lowering effects.

MR ASAP, a multicenter randomised controlled trial, set out to investigate the effect of applying transdermal nitroglycerin patch within 3 hours of symptom onset on disability in patients with suspected acute ischemic stroke or intracerebral hemorrhage.

Eligible patients with presumed stroke and initial systolic blood pressure of ≥ 140 mmHg were randomly allocated to either transdermal nitroglycerin (5 mg/day for 24 hours) plus standard care or standard care alone. Nitroglycerin patch was administered on the ambulance and continued after hospital arrival.

The study originally aimed to enroll 1,400 patients and primary outcome was 90-day disability. "In February this year, after the inclusion of 326 patients, the data and safety monitory board advised to stop recruitment for safety reasons.", explained Ms Uniken Venema, lead author for this study. The trial was then terminated in June 2021 for futility. "Based on MR ASAP data, there is no evidence of benefit of nitroglycerin in the first 3 hours of symptom onset in prehospital stroke."

The Flying Intervention Team for Endovascular Treatment Study

Flying the team of experts to deliver clot retrieval treatment for stroke patients living in remote areas. Does it work?

Clot retrieval, also known as endovascular treatment (EVT), is a highly effective therapy for acute ischemic stroke. Effect on outcome is time dependent. Therefore, treatment should be initiated as fast as possible.

EVT can only be delivered by highly skilled experts, which are not always available in hospitals in remote areas. Consequently, rural stroke patients experience significant treatment delays and worse outcomes. A model of skilled experts transported via helicopter to deliver EVT to stroke patients in rural hospitals, the Flying Intervention Team (FIT), was tested and compared to the standard model of transferring patients from rural hospitals to urban intervention centers.

In a prospective registry-based observational study in Germany, consecutive patients of 13 rural hospitals were recruited over a three-year period (2018-2021) during which FIT service was available for 26 weeks each year. Results showed that more patients in the FIT group received EVT compared to the transfer group. EVT was initiated approximately 1.5 hours faster in the FIT group than the transfer group. A trend towards better functional outcome at three months was observed in the FIT group but did not reach statistical significance.

FIT is a promising model for stroke patients living in remote areas. Further evaluation is needed to determine if FIT leads to better clinical outcome and whether this system can be applied in other regions and health care systems.

MR CLEAN-MED Trial:

Could antithrombotic drugs administered during endovascular therapy (EVT) improve distal reperfusion and improve clinical outcomes in acute large artery ischemic stroke patients?

EVT is an effective procedure for restoring blood flow to the brain in acute ischemic stroke. However, many patients do not recover despite rapid and complete opening up of the larger blood vessels (macrovascular reperfusion). To address this shortcoming, intravenous antithrombotic drugs are often used additionally during EVT. Little is known about the risk and benefit of this approach due to the lack of randomised controlled trial evidence.

MR CLEAN-MED, presented today at ESOC 2021, examined whether periprocedurally administered antithrombotic drugs (aspirin or heparin) could improve clinical outcomes after EVT.

MR CLEAN-MED was a prospective randomised multicenter trial which included patients with ischemic stroke within 6 hours of symptom onset who also had confirmed anterior circulation large vessel occlusion.

Patients were randomly allocated to one of the following periprocedural therapy regimens: (1) no aspirin (ASA) or intravenous administration of 300 mg as a bolus, (2) no heparin or unfractionated heparin (UFH) in moderate (5,000 IU as a bolus at 1,250 IU/hour for 6 hours) or low doses (5,000 IU as a bolus at 500 IU/hour for 6 hours). The target enrollment was 1,500 patients. The primary endpoint was disability at 90 days. Safety endpoints included symptomatic intracranial hemorrhage and death.

Both the ASA and UFH therapy arms were stopped early because of safety concerns. Periprocedural treatment with ASA or UFH was associated with an increased risk of symptomatic intracranial hemorrhage. There was no evidence of a beneficial effect in either the aspirin or heparin groups regarding the functional outcome.

The study authors, Van der Steen and colleagues, advise against the use of ASA and UFH in the evaluated dosages during endovascular therapy due to an unfavorable risk-benefit ratio.

SWIFT DIRECT trial – A preliminary analysis

Is giving intravenous thrombolysis (t-PA) ahead of clot retrieval therapy in acute ischemic stroke really necessary?

Mechanical thrombectomy (MT) or clot retrieval is an established and effective endovascular therapy for patients with acute ischemic stroke due to large vessel occlusions. First randomised controlled trials (DIRECT MT, DEVT) have suggested that direct MT (without pretreatment with t-PA) is non-inferior to (not

worse than) the combined approach with additional intravenous t-PA administration. Nevertheless, whether pretreatment with t-PA is beneficial remains unresolved - this could change soon.

The multicenter randomised SWIFT DIRECT trial investigated whether direct MT alone is non-inferior to (not worse than) MT combined with pretreatment with t-PA (administered within 4.5 hours after symptom onset) in patients with ischemic stroke due to proximal occlusions of the anterior circulation (i.e., internal carotid artery or M1 segment of the middle cerebral artery).

An analysis of preliminary data including 404 patients did not show statistical non-inferiority of direct MT over the combined approach with t-PA. Postinterventional reperfusion was high in both treatment arms and significantly higher in patients with MT plus t-PA than MT alone (97% vs 91%). Regarding safety, the rates of symptomatic intracranial haemorrhage were low in both treatment groups but significantly lower in the direct MT group (1.5% vs 4.9%). Good outcome was high in both treatment arms, with the point estimate in favour of MT plus t-PA (65% vs 57%).

Direct Mechanical Thrombectomy versus Bridging Therapy – Preliminary results of a cumulative study-level meta-analysis

The preliminary results of the latest meta-analysis by the IRIS collaborators (Improving Reperfusion strategies in Ischemic Stroke) comprehensively summarise the current knowledge on direct mechanical thrombectomy (MT) compared to bridging therapy based on the five largest randomised controlled trials available.

The studies included were DIRECT MT, DEVT, SKIP, MR CLEAN noIV, and the latest findings from SWIFT DIRECT. The aim was to compare the pooled effects of direct MT with intravenous thrombolysis plus MT on functional independence (mRS 0-2) at 90 days in patients with acute large vessel ischemic stroke. All studies had a non-inferiority design (with MR CLEAN noIV having this as a secondary outcome only) with different non-inferiority margins applied. Two trials achieved non-inferiority (DIRECT MT, DEVT), three did not.

For the random-effect meta-analysis, six non-inferiority margins were determined for the risk difference for functional independence at 90 days (ranging from -15% to -1.3%). The pooled analysis showed a risk difference in good functional outcome (mRS 0-2) of -1.3% (95% CI -5.6, 2.9), suggesting that direct MT is non-inferior to the combined approach using bridging therapy - except for the more stringent non-inferiority margins. Successful reperfusion was greater after MT with bridging therapy compared to direct MT alone. Regarding safety, higher haemorrhage rates were observed in the MT group with bridging therapy, whereas there was no evidence for a difference in mortality between both groups.

Urs Fischer, who presented the preliminary results on behalf of the IRIS collaborators, concluded: "Individual patient data meta-analyses are urgently needed to identify subgroups of patients who respond better to one of the treatment strategies in order to individualise future therapies."

ENDS

Notes to Editors:

A reference to the European Stroke Organisation (ESO) Conference must be included in any coverage or articles associated with this study and research.

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About ESO:
The European Stroke Organisation (ESO) is a pan-European society of stroke researchers and physicians, national and regional stroke societies, and lay organisations, founded in December 2007. The ESO is an NGO comprised of individual and organisational members. The aim of the ESO is to reduce the burden of stroke by changing the way that stroke is viewed and treated. This can only be achieved by professional and public education and making institutional changes. ESO serves as the voice of stroke in Europe, harmonising stroke management across the whole of Europe and taking action to reduce the burden.