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The virtual ESO-WSO 2020 Conference, jointly organised by the European Stroke Organisation and the World Stroke Organization, presents latest stroke research results and developments.

AFFINITY: The AFFINITY ('The Assessment oF FluoxetINe In sTroke recoverY') reports that taking Fluoxetine 20mg daily for 6 months after acute stroke did not offer a better functional outcome than placebo. Fluoxetine increased the risk of falls, bone fractures, or seizures at 6 months but not at 12 months after stroke. This trial does not support the routine use of fluoxetine after acute stroke.

EFFECTS: The EFFECTS ('Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke') trial found that 20mg of fluoxetine (an SSRI antidepressant) for 6 months did not result in better functional recovery after acute stroke compared to placebo. Fluoxetine reduced the occurrence of depression but increased the risk of bone fractures and low sodium levels. Routine use of fluoxetine after acute stroke is not recommended.

THALES Trial: Dual antiplatelet therapy with ticargrelor and aspirin may be more effective than a single antiplatelet agent in reducing the high risk of stroke or death after an acute ischemic stroke or TIA. The 'The Acute STroke or Transient IscHaemic Attack Treated withTicAgreLor and ASA for PrEvention of Stroke and Death' (THALES) examined this. It showed that in 11'016 patients with acute ischemic stroke or high risk TIA who received Ticagrelor + Aspirin the risk of stroke or death within 30 days was lower as compared to Aspirin alone (number needed to treat=92). The risk of severe bleeding events was higher with Ticagrelor (number needed to harm=263) but did not outweigh the benefit.

VNS-REHAB: Long-term reduced hand/arm function after ischaemic stroke is common and may be improved by Vagus Nerve Stimulation (VNS) paired with rehabilitation. VNS-REHAB compared the effectiveness of vagus nerve stimulation (VNS) paired with intense rehabilitation with sham stimulation and intense rehabilitation – the control. The trail showed a positive result: hand/arm function was significantly improved immediately after the end of the in-clinic therapy, as well as 90 days later.

EFFECTS/AFFINITY

The antidepressant fluoxetine has no positive effect on recovery after an acute stroke

Small studies and a Cochrane review analysis in 2012 suggested that taking the antidepressant fluoxetine (Prozac) daily might improve functional outcome after stroke. But three large-scale randomised, double-blind, placebo-controlled trials, two of which (EFFECTS and AFFINITY) were presented at the ESO-WSO 2020, showed no such effect on disability for stroke patients after six and twelve months.

A small study in 2011 (FLAME) involving 118 post-stroke patients reported a positive effect of fluoxetine on motor recovery after stroke. A Cochrane review of available studies in 2012 provided the rationale for

conducting large clinical trials to address the question of whether the antidepressant can improve stroke recovery.

Three large-scale efficacy studies with similar methodology were launched to answer this question, with the FOCUS trial (UK; 3,127 patients) publishing its results in 2019. In FOCUS, taking fluoxetine 20mg for six months did not improve recovery after acute stroke compared to placebo (p=0.439, i.e. no statistical significance). The treatment reduced occurrence of depression but increased the risk of bone fractures.

The EFFECTS study was conducted in Sweden. It enrolled 1,500 patients with an ischaemic or haemorrhagic stroke, 2 to 15 days after the acute event and with persisting disabilities of such severity that a medical therapy was indicated. The average age was 71 and 88% of them had suffered an ischaemic stroke. The degree of severity averaged 3 on the NIH Stroke Scale (the NIH stroke scores range from 0 to 42).

The study excluded individuals with depression, epilepsy or other contraindications. Patients were randomly allocated to take 20 mg of fluoxetine daily or a placebo for six months. At six months, the severity of disability was measured using the modified Rankin Scale (mRS: 0 – 6, increasing severity of disability with each category). The study result was neutral, showing no significant difference between the two groups (p=0.42).

Similar to the FOCUS trial results, EFFECTS reported a borderline significantly lower occurrence of a new depressive disorder in the fluoxetine group (7%) compared to the placebo group (11%) (p=0.05). As side effect, bone fractures occurred more frequently in the fluoxetine group, with a frequency of 4% (placebo group: 2 %; p=0.0058).

Very similar results emerged in the AFFINITY Study which was conducted in 1,280 ethnically diverse stroke patients in Australia, New Zealand and Vietnam. The participants were randomised within 2 to 15 days after the acute event to taking 20 mg of fluoxetine daily or placebo for six months.

The distribution of disability across the mRS classification was similar in both groups at 6 and 12 months. Once again, fluoxetine did not reduce disability after acute stroke compared to placebo (p=0.53 at 6 months, p=0.46 at 12 months). The increased risk of falls, fractures and epileptic seizures at 6 months in the fluoxetine group was no longer detected at 12 months.

In summary, all three large clinical trials (FOCUS, EFFECTS, AFFINITY) found no evidence of a positive effect of fluoxetine on stroke recovery.

THALES Trial

Platelet aggregation inhibitors for secondary prevention of ischemic strokes

Five to ten percent of patients with an ischemic stroke or a transient ischemic attack (TIA) still suffer a subsequent stroke. This risk is highest in the first month. Platelet aggregation inhibitors (referred to below as “antiplatelet agents”) such as low-dosed aspirin (acetylsalicylic acid/ASA) have been widely used to reduce recurrence rates. However, due to the remaining risk combination therapies have been investigated in the

past to further reduce this risk. The THALES Trial was designed to asses, if the combination of two antiplatelet agents (i.e. ticagrelor and aspirin) are superior to aspirin alone in preventing further strokes or death.

The large randomised, placebo-controlled and double-blind THALES Trial shows that a combination of the two agents improves the prevention effect.

The THALES investigators included in their study 11,016 patients with a high risk TIA ($ABCD^2$ score ≥ 6),a minor to moderate stroke (with an NIH stroke scale score of ≤ 5) at 414 participating study sites worldwide.

The primary outcome measure to assess effectiveness of the novel combination therapy was the frequency of stroke or death within 30 days (i.e. composite outcome). Secondary criteria were a (further) subsequent ischemic stroke and disability within 30 days. The frequency of severe bleeding events was selected as the primary outcome measure of safety.

5.4% of the patients receiving the combination therapy (ticagrelor/aspirin) had a stroke or died within the 30-day observation period. In the control group receiving aspirin alone, the endpoint of this study occurred in 6.5%. This difference was statistically significant (p=0.015) with a Hazard Ratio (HR) of 0.83 (95%CI 0.71-0.96). When assessing any stroke as an outcome the reduction in risk remained (HR 0.81, 95%CI 0.69-0.95), however this was not the case for death as an outcome (HR 1.33 95%CI 0.81-2.19).

A further disabling stroke occurred in 4.7% of patients in the placebo group and 4% in the ticagrelor/aspirin group (observation period 30 days). This meant a risk reduction of 17% (p=0.04). The degree of permanent impairment after secondary stroke was reduced by 23% overall. This was statistically significant.

The safety signal assessed by severe bleeding events, occurred more often in patients receiving the dual therapy (0.5%) as compared to those receiving only aspirin (0.1%) with a HR of 3.99 (95%CI 1.74-9.14, p=0.001).

From these results, the authors conclude that the combination therapy is more effective in preventing further strokes among patients with previous minor to moderate ischemic stroke or high risk TIAs compared to the single therapy with aspirin alone. The risk of severe bleeding events is clearly higher but did not outweigh the beneficial preventive effect (number needed to treat = 92; number needed to harm =263). According to the calculations, the combination therapy could prevent 11 more strokes or deaths per 1,000 people. With 4 of 1,000 a severe hemorrhage would be expected.

These results are in line with prior data investigating the short-time combination of antiplatelets (i.e. aspirin and clopidogrel) in the CHANCE and POINT trials, although the trial design and population was somewhat different.

The strength of the trial lies in the large number of patients enrolled, with a diverse number of centers and geographic locations represented. The study is moreover, the first to demonstrate a reduction in the risk of (further) disabling strokes as a result of such a combination therapy in the investigated patient group. However, treatment and follow-up only extended for 30 days so the long-term benefits and risks are challenging to assess, although risk of stroke is highest after incident event.

Only patients with high-risk TIA (ABCD^2 score ≥6) were recruited in the THALES study, while lower risk TIA patients, or patients arriving after 24 hours were excluded. It could thus be that the bleeding risk may exceed benefits conferred by the DAPT among low-risk TIA patients. Thus, it is important to exercise caution and not generalize the results. Another direct comparison of dual antiplatelet strategies in patients with TIA or minor stroke (Clopidogrel with Aspirin in High-risk Patients with Acute Non-disabling Cerebrovascular Events II [CHANCE-2]) is currently ongoing.

The THALES Trial was published in the New England Journal of Medicine (Vol. 383 No.3) on 16 July 2020. Publications on subgroup analysis are following the latest has been published in the JAMA Neurology (Amarenco P et al. JAMA Neurol. 2020; published online November 7).

VNS

Electrical Vagus Nerve Stimulation improves rehabilitation outcome

Following a stroke, many patients suffer long-term impairments, which frequently affect hand and arm function. The effect of rehabilitation therapy incorporating targeted movement training can be improved when paired with electrical Vagus Nerve Stimulation (VNS).

This study (Phase III) performed by Jesse Dawson (University of Glasgow/UK) and U.S. scientists investigated the effectiveness of a combination pairing physical rehabilitation with VNS using an implanted device. The trial included a total of 108 patients with moderate to severe upper extremity impairment after ischaemic stroke. All participants were implanted with a VNS device akin to a pacemaker, which when used, delivers electrical impulses to the vagus nerve. All participants received six weeks of in-clinic rehabilitation (followed by a home exercise program). 53 participants were randomly allocated to receive VNS (VNS group) and 55 participants were randomly allocated to receive sham VNS (control group).

The primary outcome was the function of the affected upper extremity (hand/arm) as measured by the Fugl-Meyer Assessment Upper Extremity (FMA-UE) score on day-1 post completion of the in-clinic therapy. The FMA-UE scale ranges in value from 0 for non-functional to 66 for fully functional.

The addition of VNS to rehabilitation showed a positive effect that was significant statistically. At day-1 post-completion of the 6 weeks of in-clinic therapy, the mean FMA-UE score had increased by 5.0 points for the VNS group and by 2.4 points for the control group (p=0.001).

At day-90 post completion of the in-clinic therapy, a larger proportion of patients in the VNS group (47%) showed a clinically meaningful response in motor function than the control group (24%), as measured by the FMA-UE. The difference was statistically significant (p = 0.01).

Additional information, including video interviews with principle investigators and summary slides are available on the ESO-WSO 2020 Media Portal https://eso-wso-conference.org/

Issued by the ESO-WSO 2020 PR Committee
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