Standing Out in Neurology
Nörolojide Öne Çıkanlar

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Does transcatheteric closure procedure provide secondary prevention in cryptogenic ischemic cerebrovascular patients with patent foramen ovale?

A clear underlying cause cannot be determined in up to 40% of ischemic cerebrovascular (CVH) patients in spite of detailed investigations. These patients are diagnosed with ischemic stroke of unknown cause (cryptogenic). It has long been a subject for debate whether patent foramen ovale (PFO) is a factor or not in cryptogenic CVH patients. Indeed, PFO is quite frequently encountered in the population. In autopsy series, one in four individuals is found to have PFO. This rate goes up to 56% in ischemic CVH patients below the age of 55. On the other hand, the rate of PFO among patients suffering stroke at a later age is not clearly different than that in control groups. The fact that PFO is more common in younger stroke patients supports the theory that PFO may, at least in patients of this age group, via the right-to-left shunt mechanism, follow a paradoxical embolic pathway.

Although it is observed more frequently in younger individuals, it is not clear what to do in CVH patients with PFO. Many centers suggest closure of the PFO in the second attack, if not in the first attack. With the widespread use of percutaneous use of transcatheter devices, this method is seen to be administered more commonly in the stroke patient group, although it is not registered for this use.

Furlan et al investigated the effectiveness of PFO closure in CVH patients with PFO in the CLOSURE I study ("Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale"). The study had 909 cryptogenic CVH patients between the ages of 18 and 60 randomized into 2 groups: the first group had antiplatelet treatment (6 months of clopidogrel and later aspirin) following percutaneous PFO closure, and the second group had medical treatment only. The medical treatment group was also administered warfarin, aspirin or both, based on the investigator's decision. The PFO closure procedure was unsuccessful in 14% of the patients.

At the end of two years, the rate of stroke or transient ischemic attack was found to be 5.5% in the PFO closure group and 6.8% in the medical treatment group (hazard ratio: 0.78, 95 CI 0.45-1.35; p=0.37). No death occurred in the follow-up period. The size of PFO or the presence of atrial septal aneurism did not appear to have an effect on the results.

It appeared there was a clear difference between the two groups for complications of surgical procedure. The risk of major vascular complications resulting from the procedure was 3% and the rate of atrial fibrillation was 6%.

Although the study was quite large and well planned, it had the power to detect only a 30% difference between the two groups. The clinical significance of small differences in real life setting is, indeed, controversial. The increase in the frequency of atrial fibrillation seen following the closure procedure may have played a role in the absence of a difference between the groups. In conclusion, currently it seems that closure of PFO in patients with cryptogenic stroke or transient ischemic attack is not superior to medical treatment. The effect of the procedure in PFO patients with recurrent stroke appears to be worth investigating.

References

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Does adding memantine to cholinesterase inhibitors increase the effect?

Memantine improves cognition and daily functions in moderate and severe Alzheimer's Disease (AD). Cholinesterase inhibitors, on the other hand, are mostly active in patients with mild – moderate AD. Discontinuation of cholinesterase inhibitor treatment, crossing over to memantine or combining both drugs in severe AD patients on cholinesterase inhibitor treatment is under debate. Tariot et al, in their study published in JAMA in 2004, showed that memantine added to donepezil is superior to placebo cognition, daily vital and behavioural functions. On the other hand, Porsteinsson et al observed that adding memantine to cholinesterase inhibitors did not provide an additional benefit.

Howard et al aimed to find an answer to the same question. They randomized 295 patients into 4 groups; the patients had been receiving donepezil treatment for the last 3 months, who had scored between 5 and 13 in the Standardized Mini Mental State Test (SMMST), and whose physicians were considering a change in treatment. The first group had memantine added to the donepezil treatment (donepezil + memantine), the second group received donepezil and placebo treatment (donepezil + placebo), the third group stopped receiving donepezil treatment and initiated memantine treatment (placebo + memantine) and the last group stopped receiving donepezil treatment and started receiving placebo (placebo + placebo). The patients were followed for 52 weeks. Donepezil was administered at a dose of 10 mg/day, and memantine at a dose of 20 mg/day throughout the study.

The primary endpoint of the study was observing a difference in SMMST and Bristol Activities of Daily Living Scale (BADLS) between the group. Although the study was planned to enroll 800 patients initially, due to the recruitment rate being lower than predicted, enrollment was terminated early by the proposal of the British Medical Research Council (MRC).

When the group continuing to receive donepezil (donepezil + placebo) and the group not receiving donepezil (placebo + placebo) were compared, there was a mean 1.9 point (%95 CI, 1.3-2.5; $p<0.0001$) improvement in the SMMST score and 3.0 point (%95 CI, 1.8-4.3; $p<0.001$) improvement in the BADLS score. It must be noted that the difference became apparent in the first 6 weeks that the patients started receiving the drug. When the groups receiving memantine (placebo + memantine) and not receiving memantine (placebo + placebo) were compared, there was a mean improvement of 1.2 points in the SMMST score (%95 CI, 0.6-1.8; $p<0.001$) and 1.5 points (%95 CI, 0.3-2.8; $p=0.02$) in the BADLS score in the active drug group. Although the SMMST and BADLS scores in the patients receiving donepezil and memantine combination were significantly better than the group receiving placebo (placebo + placebo), there was no statistically significant difference compared to the scores of the groups receiving donepezil alone (donepezil + placebo) or memantine (placebo + memantine).

The study appears to show that although both drugs are effective alone, there is no added benefit of combining them at the end of the first year. In addition, this trial showed that while the effect of donepezil is more apparent than that of memantine on cognitive functions, memantine is more effective on behavioural symptoms.

References

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A novel treatment for multiple sclerosis: Laquinimod

Fingolimod, the first oral treatment in multiple sclerosis (MS) introduced 2 years ago, has been threatening interferon and glatiramer acetate, used in the treatment of MS since the 1980's. Fingolimod was followed by teriflunamide that was approved by the FDA last year and is expected to be launched in the USA this year. Other oral treatments are expected to join these in the following years.

The long awaited phase III study of laquinimod has finally been published in the March issue of the NEJM. Laquinimod, a quinolin-3-carboxamide, is derived from its precursor requinimex. Raquinimex was previously tried in a phase II study in MS patients, but due to serious side effects, including myocardial infarction and pericarditis, during the treatment, the study had to be terminated early.

The ALLEGRO ("Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis") trial planned by Comi et al, had 1106 patients randomized to laquinimod 0.6 mg and placebo once a day. The trial was a follow-up study of two years. The primary endpoint of the trial was the number of attacks, and the secondary endpoints were the progression of disability, and the observation of change in the MSFC ("Multiple Sclerosis Functional Composite") and MRI parameters.

Approximately 78% of the patients completed the 2-year follow-up. At the end of the study, the annual relapse rate was 0.30 ± 0.02 in the laquinimod group, compared to 0.39 ± 0.03

in the placebo group (p=0.002). The rate of patients without an attack was 63% in the laquinimod group, and 52% in the placebo group (p<0.001). The active drug group was also better for the progression of disability (11% versus 16%; hazard ratio, 0.64; p=0.01). On the other hand, there was no significant difference between the two groups for MSFC. Laquinimod was also seen to be apparently more effective in radiological parameters, as well. The decrease in number of lesions uptaking contrast material was 63% and the decrease in the number of new or growing T2 lesions was 70% in the group receiving the drug. In addition, laquinimod decreases brain atrophy 32% (-0.87% versus -1.30%, mean difference 0.43%; p<0.001).

There was no death during the study among patients receiving active drug and there was no apparent difference between the groups for serious adverse effects. The most common drug related side effects were impairment of hepatic function tests, coughing, abdominal and back pain. In addition, it was noted that while only 1 patient had appendicitis in the placebo group, 5 patients had appendicitis in the laquinimod group.

BRAVO ("Benefit-Risk Assessment of Avonex and Laquinimod") study was planned concomittantly with the ALLEGRO study. The results of this study were presented at the ECTRIMS / ACTRIMS congress held in Amsterdam in 2011. This trial had 1300 patients randomized to laquinimod (0.6 mg/day), interferon ß-1a (Avonex®) and placebo. To the disappointment of all, the study could not reveal a difference between laquinimod and placebo in the primary endpoint, the annual relaps rate. The responsibility for this seems to fall on the difference between the baseline MRI of the two groups. When a statistical adjustment is made for the baseline MRIs, approximately 20% decrease is observed between the annual relapse rates of treatment and placebo. As for the secondary endpoints of the study, there is a 28% decrease in brain atrophy. Although interferon ß-1a showed a statistical significance for the primary endpoint, it was not effective on brain atrophy.

The results of the BRAVO study created some concern that the laquinimod dose used in the phase III studies may have been too low. Therefore, the CONCERTA study was planned where the 1.2 mg dose would be compared with the 0.6 mg dose and placebo. The results of this trial are expected to be published in the following years.

References

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