Editorial

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Surgical treatment for migraine: Time to fight against the knife

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Migraine can be a disabling disease if migraine attacks are frequent and severe (1). Frequent migraine requires preventive therapy by drug treatment (2) in combination with counselling, behavioural therapy or exercise. As in all chronic diseases, patients are inclined to search for the ultimate treatment that supposedly cures the condition. Here comes the attraction of surgical or interventional therapy. Patients with poor understanding of the complex pathophysiology of migraine tend to believe that surgical or interventional procedures might be effective in migraine with only minor or no long-term adverse events and fail to apply the necessary lifestyle modifications. In this editorial we will briefly discuss the missing evidence for the surgical treatment of trigger sites, chronic bilateral occipital nerve stimulation (ONS) and patent foramen ovale (PFO) closure and discuss the impact of the placebo effect in studies with surgical interventions.

Surgical treatment of trigger sites

For a European it is impressive to visit a website in the United States (US) called "American Migraine Center" (http://americanmigrainecenter.com/in-the-news/surgical-treatment-of-migraine-headaches/) The website promotes the surgical removal of migraine trigger sites and claims: 'However, more and more, Dr. Guyuron is achieving complete elimination because of his experience in detecting the trigger sites and some refinements in the techniques that he has implemented over the last ten years since he began doing this surgery'. Do we not all dream of the ultimate way to 'cure' migraine? Let us have a closer look at this procedure: Guyuron et al. published two papers reporting results of a placebo-controlled surgical trial of the treatment of migraine headaches (3,4). He screened 317 patients with migraine and treated 130 of them with botulinumtoxin type A at 'trigger' points. Seventy-six patients responded to botulinumtoxin type A and underwent surgical resection of frontal, temporal or occipital triggers or a sham procedure (randomisation ratio 2:1). No information is provided on how patients were selected, what prior treatment had been used and whether any patients had medication-overuse headache. No data are provided on co-morbidities that are frequent in severe migraine such as depression or anxiety disorders. The use of botulinumtoxin type A to select patients clearly selects patients prone to respond to placebo. In episodic migraine, botulinumtoxin type A is not superior to placebo (5). Therefore it is difficult to understand how patients were selected for the surgical procedure. The sham procedure was not really sham, since it resulted in sensory or motor deficits. The study was underpowered and did not follow International Headache Society (IHS) guidelines for the selection of the primary endpoint. The authors used a headache index which leads to skewed distributions. The statistical analysis did not account for this, did not correct for multiple comparisons and did not consider possible imbalances at baseline. Finally, the study had a 'cure' rate of 57%, never seen before in the history of migraine treatment. This was a single-centre trial and the results were not replicated by another randomised study. We present this study in lectures for students at our medical school as an excellent example of how a flawed study design and inappropriate statistical analysis can produce nonreproducible results. In our country we were successful in convincing the insurance companies to not reimburse this procedure.

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Chronic ONS for the treatment of chronic migraine

ONS was introduced as a treatment method for occipital nerve neuralgia (6). The observation that some migraine patients would respond for some time to a local block of the occipital nerve prompted the introduction of ONS for the treatment of treatment refractory or chronic migraine. A feasibility study sponsored by Medtronic Neuromodulation USA included 75 patients with intractable chronic migraine >15 headache days per month (7). The study was not powered to detect statistically significant differences in outcomes. The responder rate (improvement of headache days >50%) was 39% with adjustable stimulation ($n=28$), 6% ($n=16$) with preset stimulation and 0% ($n=17$) in medically managed patients at three months. Lead migration occurred in 12 of 51 subjects (24%).

The study by Silberstein et al. (8) investigated ONS in patients with chronic migraine refractory to treatment of acute migraine attacks and having failed at least two different classes of prophylactic medication. A total of 157 patients received ONS device implants, and 105 patients were randomised to active and 52 to sham stimulation. The study failed to show a significant benefit for the primary endpoint, a ≥50% reduction in mean daily visual analogue scale score after 12 weeks. The study was positive for a number of secondary endpoints, including 30% reduction in mean daily visual analogue scale scores, number of headache days, and migraine-related disability. Rare but clinically relevant adverse events were lead migration (13%) and consistent implant site pain or numbness (15%).

Experience from centres which apply this technique show a response rate that is lower in chronic migraine than in chronic cluster headache. In addition, long-term complications, especially local infections, occur in up to 20% of patients (personal observation).

PFO closure for migraine prevention

This topic emerged when several case-control studies reported a possible link between PFO and migraine. Several studies confirmed by different methods (transcranial Doppler ultrasonography, transesophageal echocardiography) the relationship between PFO and migraine with aura (9). The association of PFO with migraine without aura and other headaches is weak. A meta-analysis from 2013 included 37 studies (10). The overall pairwise associations between PFO, cryptogenic ischemic stroke and migraine did not suggest a causal role for PFO. Studies with population-based comparators showed no association between migraine with aura or PFO (odds ratio (OR) 1.0; 95% confidence interval (CI) 0.6–1.6; one study). The most likely explanation is that both conditions, migraine with aura and PFO, could be dominantly inherited and share a common genetic background (11).

Several retrospective studies found a relationship between PFO closure and migraine improvement. However, with one exception, all of these studies had major limitations. Migraine improves spontaneously with age, and no study had a control group. The high placebo response rates associated with interventional treatments can reduce the frequency of migraine (see below). After PFO closure, most patients received aspirin, which has a modest migraine prophylactic activity, at least in men (12). Most studies were based on retrospective collection of headache data, which is highly unreliable; recall bias has a major influence on the results. Furthermore, a more recent study observed that as many patients experience migraine improvement as experience new-onset migraine after PFO closure (13).

To date, only one randomised and controlled prospective trial examining this issue has been performed, in the United Kingdom. The Migraine Intervention with STARFlex Technology (MIST) trial recruited patients with frequent migraine with aura that was refractory to preventive treatment (14). The trial randomly assigned 147 patients to undergo either transcutaneous PFO closure with a STARFlex septal repair implant (NMT Medical, Boston, MA, USA) or a sham procedure. The primary endpoint, cure of migraine, was not significantly different between the two treatment groups. There was a nonsignificant trend for a reduction of migraine frequency in the group that received PFO closure. Serious adverse events including cardiac tamponade, pericardial effusion, retroperitoneal bleed, atrial fibrillation, and chest pain were also seen.

At present there is insufficient evidence to support the hypothesis that migraine frequency is improved by PFO closure. Nevertheless this procedure is still performed and promoted by interventional cardiologists. Considering the negative outcome of a large randomised trial, this raises major ethical concerns.

The role of placebo in interventional headache treatments

Placebo effects substantially contribute to treatment outcome in headache and other pain disorders. These effects are not mediated by the sham treatment itself, but by the patients' expectations regarding its effect and prior treatment experiences. Learning processes mediating placebo effects do not necessarily have to be based on first-hand experience but can also be the result of social observational learning (15) and are highly influenced by the public media.

In the past decades intensive neuroscientific investigations have shown that subjective symptom improvement (e.g. pain relief) during placebo treatments has complex neurobiological (16) and peripheral physiological substrates (17).

Importantly, placebo effects occur not only when placebo (inert) treatments are performed. Expectation and learning also substantially modulate the response to active treatments. This was illustrated in a recent prospective, controlled study on the effect of placebo and rizatriptan for acute migraine in which treatment expectation (induced by different drug labels) substantially increased the effect both of placebo and rizatriptan. Rizatriptan labelled as placebo and placebo labelled as rizatriptan had similar effects and relative to no treatment, the placebo accounted for more than 50% of the drug effect (18).

While in clinical care placebo mechanisms (i.e. expectation and learning) should be harnessed to improve the efficacy of therapeutic strategies, they can substantially distort the results of clinical trials, particularly if placebo effects are not properly controlled for in each treatment arm (19,20). Invasive treatments, particularly treatments inducing sensory sensations (i.e. acupuncture, injections), are known to show substantially larger placebo responses compared to oral treatments (21,22). Impressive examples of this are the substantial reductions in migraine frequency following saline injections in the Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials.

At the same time, sensory symptoms induced by the treatment bear the risk of unblinding and subsequently heightened treatment expectations as often the control condition (sham surgery or sham stimulation) is perceived differently. Imbalanced randomisation schemes with more patients receiving the active compared to the control treatment further contribute to substantial distortions/skewing of the outcome in clinical trials.

These aspects should receive more consideration in the conception and interpretation of clinical studies involving invasive headache treatments.

The future of interventional migraine treatment

Does 'surgical' migraine prevention have a role in future? We think the highest priority should be the implementation of integrated headache care in headache centres to help patients with chronic migraine with and without medication overuse. We doubt that 'treatment-refractory' migraine patients really exist. We see no role for the surgical resection of trigger sites. There is no pathophysiologic rationale for this approach. The same is true for PFO closure. Migraine is disabling but not life threatening. PFO closure can lead to severe adverse events. The efficacy of ONS stimulation has not been proven for chronic migraine. Here we would need more randomised studies with sham stimulation acknowledging how difficult it is to blind patients and investigators for this therapy.

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