Transorbital alternating current stimulation in optic neuropathy

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Statement of the DOG and BVA on "Gall C et al. Alternating Current Stimulation for Vision Restoration after Optic Nerve Damage: A Randomized Clinical Trial. PLoS One 2016"

Transorbital transcutaneous electrostimulation therapy has been offered for some time to improve vision in neurodegenerative optic nerve disorders, including glaucoma and age-related macular degeneration (www.savir-center.com). An article based on a multicenter, prospective, randomized and placebo-controlled study was published in June 2016 in the journal PLoS One (1) on the efficacy of this treatment in optic neuropathy. Treatment consisted of a series of daily 50-min sessions of transorbital alternating current stimulation just above the phosphene threshold over a period of 10 weeks. A placebo (sham) group received reduced frequency stimulation. A visual field improvement of 24.0% was reported with high-resolution perimetry compared to 2.5% in the sham group. According to the authors, the treatment had no relevant side effects. They concluded: "This class 1 evidence suggests that visual fields can be improved in a meaningful way."

Numerous enquiries from colleagues, as well as from the press, prompted a review of this particular publication. For the following reasons, the DOG and the BVA are unable to concur with the above-mentioned conclusions:

1. The perimetry method used

The primary endpoint of the study was measured using high-resolution perimetry. This diagnostic method was developed by the authors themselves and does not correspond to conventional perimetry techniques used in clinical practice and in studies by other groups and is not recognized by the regulatory authorities. Hence, the information currently available on this procedure does not allow a scientifically sound judgement to be made on its relevance. Since the diagnostic method is not a generally established technique, it is not possible to scientifically evaluate the described improvement of 24% in detection accuracy. In order to ensure better reproducibility and comparability of results, the DOB and BVA recommend the use of established perimetry techniques in the future.

2. Fixation control

It was performed in high-resolution perimetry in only one of the three test centers by means of objective recording of the eye position. The other two centers used a method for which reliable central fixation has not yet been demonstrated.

3. Interpretation of the treatment effect

The difference in detection accuracy between baseline and day 2 following treatment was statistically significant if one considers the entire visual field, but not if one considers the defective area of the visual field ($p = 0.13$). Therefore, it was not possible to exclude the possibility that improvement had occurred only in the unaffected area of the visual field.

4. Endpoint definition

When the study was registered in the Clinicaltrials.gov database (NCT01280877), the primary outcome measure was given as improvement in the defective visual field. However, another primary endpoint is stated in the publication, i.e. improvement in the whole visual field. This means that the primary endpoint was changed while the study was ongoing. Changing the primary endpoint retrospectively is in principle possible, for example in cases where a measurement proves to be overly complex. However, the reasons for such changes need to be provided and explicitly documented in a supplement to the study protocol. This is not the case with the article in question. It must therefore be concluded that the originally defined primary endpoint was not achieved.

5. Significance of the results and multiple testing

The results of static and kinetic perimetry with a total of five parameters, as well as near and far visual acuity were used as secondary endpoints. Together with the eight high-resolution perimetry parameters, a total of 30 statistical comparisons were made (15 directly after therapy and 15 at 8 weeks). In such cases, the significance threshold needs to be corrected using a conventional procedure (e.g., Bonferroni or Holm) (3). The article makes no mention of this.

6. Comparison of the two study arms

The two study arms differed in size (45 vs. 37). Vision also differed (in automatic static perimetry, the mean threshold—we assume that the mean sensitivity was meant here—was 11.95 dB in the sham group and 8.78 dB in the treatment group). With this imbalanced distribution, the two groups do not have the same potential for improvement. Furthermore, patients in whom spontaneous disease resolution was described were included (4).

DOG and BVA recommendations

Unless these methodological limitations have been addressed in further investigations, the proof of efficacy of the method in the manner described cannot be regarded as confirmed. In summary, the DOG and BVA conclude that the study in question does not produce the evidence required to recommend this method of transorbital alternating current therapy to improve function in optic neuropathy.

References

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