TECHNICAL TALK

REPETITIVE TRANSORBITAL ALTERNATING CURRENT STIMULATION



Could this noninvasive therapy be used to activate viable but poorly functional retinal ganglion cells in patients with glaucoma?

BY JOEL KOVOOR, BS; JOSEPH F. PANARELLI, MD; AND JOEL S. SCHUMAN, MD

As one of the leading causes of irreversible blindness, glaucoma is notorious for its insidious nature: The disease often develops and progresses undetected before symptoms present. Glaucoma is characterized as a chronic optic neuropathy associated with a rise in IOP, which leads to the selective damage of retinal ganglion cells (RGCs). Subsequent apoptotic damage of RGCs at the lamina cribrosa extends beyond the retina and upstream to cortical networks, resulting in visual field (VF) defects.[1]

Currently, IOP is the only modifiable risk factor proven to affect the progression of VF loss in glaucoma.[1] Beyond the medical and surgical management of IOP, there are no widely used clinical therapies aimed at preventing damage to or restoring RGCs at the neuronal level. However, in the research sphere, the principles of neuroplasticity and neuroprotection have been explored as possible intervention points.

AT A GLANCE

- Electrical stimulation therapy procedures such as repetitive transorbital alternating current stimulation (rtACS) recently emerged as a potential approach to influencing neuroplasticity.
- rtACS is thought to influence neuronal physiology through the synchronization of neuronal networks via low-intensity sinusoidal waveforms. With repetitive treatment, the endogenous oscillating elements of neuronal networks are entrained over time to match exogenous stimuli in damaged retinofugal pathways.
- Investigators are conducting a multisite randomized clinical trial to explore the influence of rtACS on neuronal morphology and physiology to improve patients' visual function, functional ability, and quality of life.

NEUROPROTECTION AND NEUROPLASTICITY

Neuroprotection refers to any intervention that prevents optic nerve damage, and it has yielded mixed results. Neuroprotective agents come in oral and topical forms. They include alpha-2 adrenergic agonists, calcium channel blockers, brain-derived neurotrophic factors, and nitric oxide synthase inhibitors.[2] A review of various neuroprotective agents demonstrated that, despite promising preclinical results, the clinical application of such agents was ineffective for preventing RGC death and preserving VFs in patients with open-angle glaucoma.[2]

Neuroplasticity refers to the brain's ability to reorganize synaptic connections in response to disease, learning, and injury. This mechanism shows promise as an intervention point, especially in light of the residual vision activation theory,[3] which holds that areas of the retina damaged by disease and injury house cells with partial visual capacity. Because an injury early in the visual pathway affects upstream neural networks, the extent of damage to these residual cells determines the strength of upstream neural connections in the brain and optic nerve. These connections, in turn, influence the processing and transmission of visual information.[4] The aim of intervention in the context of neuroplasticity is therefore to activate residual neuronal capabilities in areas of reduced vision.

ELECTRICAL STIMULATION THERAPY

Electrical stimulation therapy (EST) recently emerged as an approach to influencing neuroplasticity. First clinically implemented by Bechtereva and colleagues in 1985, EST procedures have expanded from the surgical implantation of electrodes in the optic nerve to noninvasive techniques such as repetitive transorbital alternating current stimulation (rtACS).[5]

First employed clinically in a case study of a patient with a posttraumatic optic nerve lesion, rtACS is thought to influence neuronal physiology through the synchronization of neuronal networks via low-intensity sinusoidal waveforms.[6] With repetitive treatment, the endogenous oscillating elements of neuronal networks are entrained over time to match exogenous stimuli (ie, rtACS frequency) in damaged retinofugal pathways.[7,8] These treatments are believed to be bandwidth-specific to the alpha frequency, which is thought to be physiologic to visual networks in the brain and has been shown to be decreased in individuals who are congenitally blind.[9,10]

The effect of rtACS on VFs has been demonstrated in various trials and in patients with various optic neuropathies. Specifically, in a retrospective analysis of 446 patients with optic nerve damage from traumatic brain injury, inflammation, brain tumors, and vascular lesions, patients treated with rtACS experienced a significant increase in VFs (right eye, 7.1%; left eye, 9.3%; $P < .001$), as measured by kinetic perimetry.[11]

Further, in a 2016 multicenter randomized controlled trial (RCT) comparing rtACS with sham treatment in an undifferentiated group of patients with optic neuropathy primarily from glaucoma and anterior ischemic optic neuropathy, a significant mean improvement in VFs was observed in the rtACS group compared with the sham group (24% vs 2.5% change; $P = .011$).[12] This was consistent with a smaller 2011 masked RCT of patients with undifferentiated optic neuropathy, which also showed significantly greater detection accuracy of defective VFs ($P = .03$) in the rtACS group.[13]

rtACS has also shown promise for long-term VF improvement. In the aforementioned 2011 retrospective analysis, patients experienced insignificant decreases in VF performance 6 to 9 months after rtACS treatment, suggesting a long-lasting neural adaptive process even in the absence of an exogenous stimulus.[11] When patients underwent a second round of rtACS, their VFs remained significantly improved in both eyes compared with baseline.[11] This finding was confirmed by the 2011 RCT, in which rtACS showed significantly better detection accuracy of the entire VF compared with sham at 2 months.[13] The 2016 multicenter RCT also demonstrated progressively improved detection accuracy in the entire VF and mean threshold compared with sham treatment.[12]

Results were more mixed in terms of improvements in visual acuity (VA). In the 2011 RCT, VA improved significantly at both near and far ($P < .05$), whereas the 2011 retrospective analysis showed improvement only for distance VA ($P < .01$).[11,13] The 2016 multicenter RCT showed no significant improvement in VA after intervention in the rtACS group compared with the sham group.[12]

Although improvements in VFs are promising, data on quality of life (QOL) measurements have not been established. Gall and colleagues explored this in a randomized pooled analysis comparing QOL measurements between rtACS and sham treatment in patients with undifferentiated causes of optic neuropathy.[14] Subjective vision-related QOL measures were characterized with the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and more general health QOL measures were characterized by the Short Form Health Survey (SF-36). Although composite NEI-VFQ scores did not differ significantly between rtACS and sham groups, there was a significant improvement for the rtACS group in NEI-VFQ measures for certain subdomains, including general vision, distance activities, and social functioning.[14] Further, patients in the rtACS group showed significant improvement in SF-36 measures of mental health and mental competency.[14] Nevertheless, there was no significant correlation between SF-36 QOL domains and gains in VF and only weak positive correlations with some NEI-VFQ subdomains and gains in VF.[14]

EST AND GLAUCOMA

Despite some promising early findings on rtACS, no known studies have looked exclusively at the effects of rtACS in patients with glaucoma. Preliminary data have been mixed for other forms of EST, such as transcorneal electrical stimulation (TES). In a recent pilot study by Ota and colleagues,[15] repeated TES treatment resulted in a significant positive linear relationship between changes in mean deviation and the number of TES treatments ($R^2 = .176$; $P = .005$). However, the study showed no significant change in mean deviation, IOP, or VA before and after treatment. Similar variability was reported in a small randomized study of 14 patients. IOP was found to be significantly higher in individuals undergoing TES at 66% stimulation compared with the 0% stimulation sham group ($P = .04$); no significant difference was observed with the 150% stimulation group.[16]

CONCLUSION

In response to the mixed data from TES trials and an absence of rtACS data exclusive to glaucoma, investigators at New York University are conducting a multisite RCT to explore the influence of rtACS versus sham stimulation on neuronal morphology and physiology to improve patients' visual function, functional ability, and QOL. The hypothesis for the study is that rtACS will activate viable but poorly functional RGCs to improve their structural and functional capabilities. Improvement in visual function should correspond with improvements in retinal, optic nerve, and visual brain structures, as measured by OCT, OCT angiography, MRI, and visual evoked potential. QOL measures should also improve with visual function after rtACS. This study should provide valuable insight into the clinical application of rtACS as a novel treatment for patients with visual dysfunction secondary to glaucomatous optic neuropathy. ■

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