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Editorial

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The Time is Now for Visual Electrophysiology

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Clinical visual electrophysiology, such as electroretinograms (ERG) and visual evoked potentials (VEP) have been available clinically for decades. The tests are often ordered as adjuncts to more typical clinical examination and offer the ability to determine the site(s) in the visual pathway that are affected by ocular pathology (i.e. retinal versus cortical). Suspected retinal dystrophies and cases of unexplained vision loss are often referred for visual electrodiagnostic testing. A full-field ERG, for instance, is necessary to definitively describe and diagnose retinitis pigmentosa as the clinically visible retinal findings are not always typical (e.g. retinitis sine pigmento).

The primary outcome measures of large randomized control trials of ophthalmologic pathologies have not changed for decades and traditionally have never included electrophysiological measurements as outcome measures. For instance in the first large diabetic retinopathy studies, Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), initiated in the early and late 1970's, respectively, the primary outcome measures were a doubling of the visual angle and photographic progression of the condition [1,2]. Even in some of the most recent trials, such as the PKC-DRS the outcome measures were similar [3].

It has been argued for some time that more sensitive, objective, quantifiable measures should be used as current outcome measures are often consider end-stage [4]. Over the last several years, an increasing number of trials have used electrophysiological measures as outcome measures, often times secondary ones. These are objective, quantifiable measurements of retinal function. Some feel that electrophysiological measures may be no better than LDL levels in evaluating therapeutics for risk reduction in stroke (i.e. the best outcome measure should be visual impairment or blindness) [5]. So-called surrogate outcome measures have been the subject of much discussion in the literature. However, several ophthalmic pathologies can progress to sight threatening stages without noticeable subjective or gross declines in vision (e.g. diabetic retinopathy and glaucoma). Often times the progression to the endpoint of visual impairment and blindness can occur rapidly. There is, in a sense, a geometric time progression of clinical disease rather than a linear one.

There has also been controversy with accepting electrophysiological measures as outcomes measures for disease since often times they do no correlate perfectly with standard psychophysical measures (e.g. visual acuity). Anatomical measurements such as with optical coherence tomography also do not always correlate well with subjective psychophysical measurements (i.e. visual acuity and macular thickness) [6]. Additionally, in the past standardization of visual electrophysiological recordings was lacking, but this is actively being addressed by the International Society for Clinical Electrophysiology of Vision [7,8]. With electrophysiological measurements the reliability (test-retest variance) can sometimes be high and it may be difficult to conduct multi-center trials as normative values can vary from center to center. Recently, a multicenter trial using ERGs as primary endpoint was conducted which may be a model for future trials as several issues were accounted for, such as using a single normative database between all of the clinical centers that utilized standardized equipment [9].

Examination of clinical trials registered with the National Institute of Health (USA) at clinicaltrials.gov reveals the current status of the debate. Using 'electroretinogram' as a search term for outcome measures reveals that only 3 studies before 2007 are listed. From 2007 and onward, nearly 23 studies are listed as having 'electroretinogram' as an outcome measure, nearly an 800% increase! These studies are examining many different ocular pathologies: diabetic macular edema, congenital stationary night blindness, macular degeneration, central retinal vein occlusion, and uveitis to name a few.

Electrophysiology offers an objective, quantifiable, non-invasive assessment of neural function and its use in clinical trials has been gaining use at a rapid pace. Clinicians and scientists need to further their understanding of this area of ophthalmic evaluation, understanding the challenges, but also realizing that they can be overcome. The continued use the current conventional endpoints in clinical trials may ultimately hinder drug development for ocular pathologies, if it has not already. The time is now.

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