Assessing nonsedated handheld cone flicker electroretingram as a screening test in pediatric patients: comparison to sedated conventional cone flicker electroretinogram

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PURPOSE To assess the RETeval (LKC Technologies, Gaithersburg, MD) handheld electroretingram (ERG) device as a screening tool for cone dysfunction in pediatric patients by comparing it to conventional ERG.

METHODS Patients scheduled for ERG under general anesthesia (GA) underwent three tests: (1) RETeval standard 30 Hz cone flicker ERG using skin electrodes prior to GA, (2) E3 Diagnosys (Diagnosys LLC, Lowell, MA) conventional complete standard protocol full-field ERG using bipolar contact lens electrodes and handheld stimulus under GA, and (3) repeat RETeval testing under GA. The 30 Hz cone flicker amplitudes and implicit times from the three methods were compared. Negative and positive predictive values were calculated by applying a previously established 5 μV amplitude cut-off.

RESULTS Thirty patients ≤18 years of age were enrolled. Impaired conventional ERGs were found in 18 patients. Compared to conventional ERG under GA, RETeval cone flicker amplitudes were smaller before GA (mean difference, -42.2 ± 45.3 μV) and under GA (-37.1 ± 44.5 μV), likely due to skin electrode; and implicit times were shorter before GA (-1.06 ± 2.83 ms) and longer under GA (1.28 ± 4.12 ms), likely due to GA. Comparing RETeval responses before and under GA, the amplitudes were lower (-3.05 ± 6.82 μV), and implicit times were shorter (-2.25 ± 3.28 μV) before GA. Overall, the positive predictive value of the RETeval was 85%; the negative predictive value, 90%.

CONCLUSIONS The unsedated handheld RETeval 30 Hz cone flicker ERG is a feasible screening test for detecting cone dysfunction in pediatric patients. Full-protocol ERG is needed when screening ERG is reduced, equivocal, or clinically warranted. (J AAPOS 2019;23:34.e1–5)

A child with low vision and a normal ophthalmic examination presents a diagnostic challenge.[1] The ophthalmologist relies on clinical findings and family history, and electroretinography is often helpful in providing a definitive diagnosis. The standard full-field electroretinogram (ERG) is currently the clinical gold standard for diagnosing hereditary retinal disorders.[2,3] With the advancement of gene therapy and the potential for treatment, identifying retinal disorders in a timely manner is imperative.[4]

Electroretinography in children poses several challenges, including limited cooperation for the test and an inability to tolerate the contact lens electrode. Therefore, general anesthesia (GA), which may affect the ERG, is often required for successful testing.[5,6]

The RETeval system (LKC Technologies, Gaithersburg, MD) is an FDA-approved, portable, handheld ERG device that uses adhesive skin electrodes and obtains cone flicker ERG readings in <1 minute. The RETeval ERG has shown good sensitivity and specificity for detecting retinal disease in both adults and children.[7-12] In a study of 71 children, we found nonsedated RETeval cone flicker ERG amplitudes and implicit times could be successfully obtained in 65 (92%) children.[12] Of the 15 children with nystagmus and 19 children without

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nystagmus, we found that an amplitude <5 μV warrants further evaluation with full-protocol ERG.[12] In the current study, we assessed the feasibility of nonsedated RETeval cone flicker ERG as a screening test in a new cohort of pediatric patients and evaluated differences in cone flicker amplitudes and implicit times between the RETeval and the sedated conventional ERG in pediatric patients undergoing GA.

Subjects and Methods

Pediatric patients (<18 years old) referred to Bascom Palmer Eye Institute, University of Miami, for scheduled full-field ERG under GA from December 2015 to June 2017 were prospectively enrolled in our study. All patients were referred by their primary pediatric ophthalmologist for suspected retinal dysfunction. The study was approved by the University of Miami's Institutional Review Board and was performed in compliance with the US Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki. After a comprehensive explanation of the procedures, informed consent was obtained from each patient's parent or guardian. Additionally, patients ≥7 years of age gave informed assent.

Each patient underwent ERG testing by three different methods: (1) ERG with RETeval prior to GA, (2) conventional ERG under GA, and (3) ERG with RETeval under GA. Prior to dark adaptation and general anesthesia, cycloplegic drops (phenylephrine 2.5%, tropicamide 0.5%, cyclopentolate 2%) were instilled in both eyes. The RETeval cone flicker ERG testing using adhesive skin electrodes was then performed. Standard 30-Hz cone flicker ISCEV parameters were followed, consisting of white flash luminance of 3.0 cd s/m^2, a background luminance of 30 cd/m^2, and flicker frequency of 28.3 Hz. Each eye was tested twice. The patient was then patched bilaterally for 45 minutes of dark adaptation before GA. With the patient under GA, an ISCEV standard full-field ERG protocol was performed using an E3 Diagnosys system with a full-field monocular handheld Ganzfeld flash stimulator and bipolar Burian-Allen contact lens electrodes. The final diagnosis was determined by the conventional ERG results, which is the accepted gold standard. Immediately after the conventional ERG was completed, ending with the cone flicker recording, a second RETeval ERG cone flicker using adhesive skin electrodes was performed under GA. Each eye was tested twice.

Statistical Analysis

For both the pre- and post-GA 30 Hz cone flicker measurements obtained with the RETeval device, the b-wave amplitudes and implicit times were calculated as the mean of the two measurements taken for each eye and based on the fundamental of the response. RETeval implicit times that were "not measurable" or with a confidence ≥1.25 ms due to extremely low amplitudes were excluded from analysis. The 30-Hz cone flicker b-wave amplitude and implicit time results obtained by conventional full-field ERG were used for analysis.

The relationships between RETeval measurements obtained while awake and under GA and with conventional ERG under GA were depicted by means of scatterplots, with the strength of correlation assessed using Pearson correlation. Amplitudes were also analyzed on a log scale, in which case a small positive constant (0.01) was added to all measurements, because 4 conventional ERGs had zero amplitude. Calculation of intraclass correlations (ICC) revealed that the two eyes of patients were moderately highly correlated (implicit times of RETeval awake and conventional ERG ICCs of 0.59 and 0.65, resp.) to very highly correlated (RETeval implicit time under GA and all amplitudes ICCs 0.82 to 1.00). Therefore, one eye of each patient was randomly selected for correlation analysis, but all eyes were included in plots. The positive predictive value (PPV) and negative predictive value (NPV) were calculated. A RETeval amplitude <5 μV[12] in either eye of a patient with abnormal conventional ERG results was considered a true positive for suspected retinal disease.

Differences between amplitudes and implicit times obtained with the RETeval and conventional ERG are presented as means with standard deviation.

Results

A total of 30 patients (57% male) were included, with a mean age of 4.2 years (range, 10 months to 18 years). The referral diagnoses were as follows: nystagmus, 16 patients; undetermined visual loss, 4; pigmentary retinopathy, 1; sensorineural hearing loss, 2; nyctalopia, 3; retinopathy of prematurity and retinal detachment of the right eye, 1; on vigabatrin therapy, 3. Of the 16 patients with nystagmus, 1 had pigmentary retinopathy, 1 had hydrocephalus and seizures, and 1 had bilateral chorioretinal colobomas.

Recordings with the RETeval device were performed on all 30 patients prior to GA and on 27 patients under GA. Implicit times were not measurable for 29 eyes prior to GA (both eyes of 13 patients, one eye of 3 patients) and for 21 eyes under GA (both eyes of 10 patients, one eye of 1 patient).

The 30 Hz cone flicker responses obtained with the conventional full-field ERG under GA were normal in both eyes in 12 patients and impaired in both eyes of 16 patients. Of the 16 patients with impaired conventional ERG, the diagnoses were as follows: retinitis pigmentosa/rod-cone dysfunction/cone-rod dysfunction, 6; achromatopsia, 4; Leber congenital amaurosis, 6. The 2 remaining patients, one with a unilateral retinal detachment and the other with bilateral colobomas, demonstrated reduced responses in one eye.

The mean amplitudes and mean implicit times recorded with each method were classified as normal or impaired (Table 1). Overall, the amplitudes recorded with the RETeval device were smaller before GA (mean difference −42.24 ± 45.30 μV) and under GA (−37.10 ± 44.45 μV) compared to the E3 Diagnosys under GA. The implicit times obtained with the RETeval were shorter prior to GA (−1.06 ± 2.83 ms) and longer under GA (1.28 ± 4.12 ms) compared to the E3 Diagnosys under GA. The RETeval amplitudes were lower (−3.05 ± 6.82 μV) and the implicit times were shorter (−2.25 ± 3.28 μV) prior to compared to under GA.

Table 1. Amplitude and implicit time values, 30 Hz cone flicker electroretinogram

	RetEval prior to GA	RetEval under GA	E3 Diagnosys under GA
Amplitude, μV, mean ± SD			
Normal	9.37 ± 4.55	16.53 ± 8.70	95.50 ± 28.80
Abnormal	2.73 ± 3.57	2.29 ± 4.03	10.42 ± 18.46
Implicit time, ms, mean ± SD			
Normal	29.17 ± 2.81	30.42 ± 1.78	29.73 ± 2.27
Abnormal	30.90 ± 3.26	39.27 ± 5.02	39.17 ± 6.85

GA, general anesthesia; *SD*, standard deviation.

Table 2. Correlations between RETeval and formal ERGs on one randomly selected eye of 30 pediatric patients[a]

Correlations	RETeval awake vs RETeval GA	RETeval awake vs E3 Diagnosys GA	RETeval GA vs E3 Diagnosys GA
Implicit time correlations (N = 17[a])			
Pearson *r*	0.468	0.525	0.534
P value	0.091	0.030	0.027
Amplitude correlations			
Pearson *r*	0.683	0.695	0.668
P value	<0.001	<0.001	<0.001
Log of amplitude correlations			
Pearson *r*	0.795	0.810	0.885
P value	<0.001	<0.001	<0.001

ERG, electroretinogram; *GA*, general anesthesia.
[a]Three patients did not have RETeval measurements while under GA; RETeval implicit time measurements did not have acceptable reliability (not measurable) in 13 eyes while awake and in 10 eyes under GA.

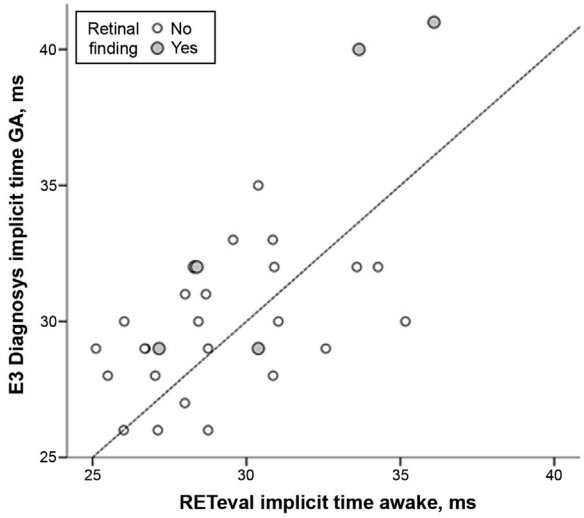

FIG 1. Scatterplot of implicit times of the conventional electroretinogram (ERG) vs RETeval (LKC Technologies, Gaithersburg, MD) prior to general anesthesia (GA).

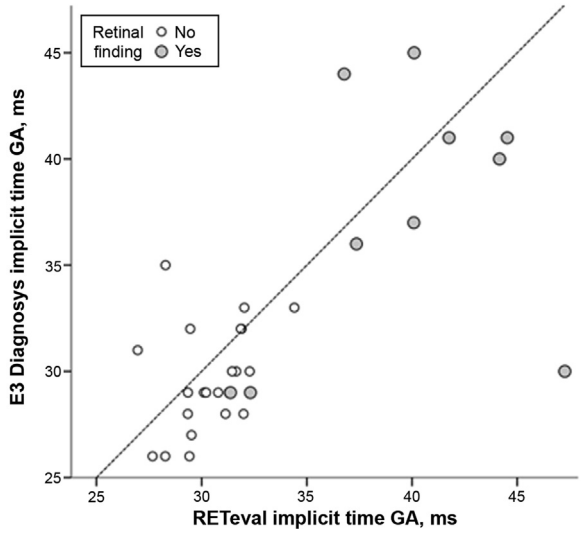

FIG 2. Scatterplot of implicit times of the conventional ERG vs RETeval under GA.

Correlations between the cone flicker ERG amplitudes and implicit times of the three methods are shown in Table 2 and Figures 1-6. Correlations were stronger among amplitude measurements (all $r > 0.66$; all $P < 0.001$) than for implicit time ($r = 0.47$-0.53; $P = 0.09$-0.02). Noticing that measurements became more variable with larger amplitudes, we also assessed these relationships on a log scale, which improved the correlations (Table 2, Figure 7).

Using the previously established cut-off amplitude of 5 μV with the RETeval,[13] there were 3 false positives and 1 false negative (Figure 4). Therefore, the RETeval had an NPV of 90% and a PPV of 85% as a screening tool for retinal dysfunction.

Discussion

Our findings support nonsedated RETeval handheld cone flicker ERG using skin electrodes as a feasible screening test for detecting cone dysfunction in children given its high PPV and NPV and the significant strong correlations of amplitudes and implicit times compared with sedated conventional cone flicker ERG using contact electrodes. Full-protocol ERG is needed when the RETeval screening ERG is reduced, equivocal, or when clinically warranted.

The RETeval 30 Hz cone flicker ERG before and under GA had expectedly lower amplitudes and shorter implicit times than the conventional cone flicker ERG responses under GA. This is because ERG amplitudes recorded with skin

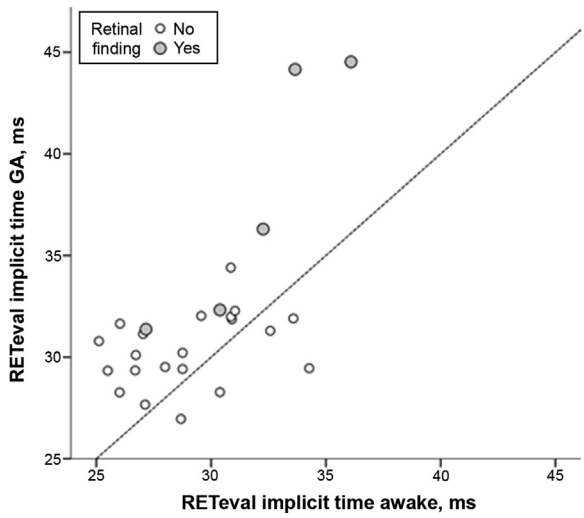

FIG 3. Scatterplot of implicit times of the RETeval under GA vs prior to GA.

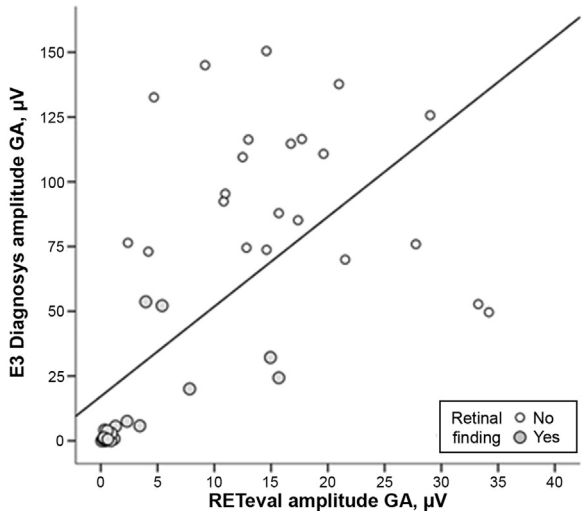

FIG 5. Scatterplot of amplitudes of the conventional ERG vs RETeval under GA.

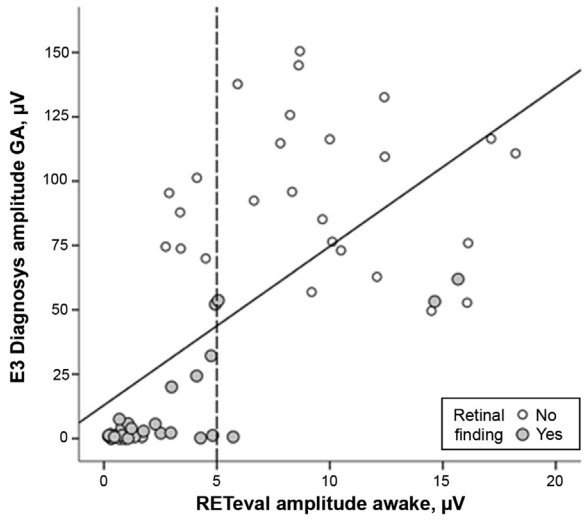

FIG 4. Scatterplot of amplitudes of the conventional ERG vs RETeval prior to GA. A RETeval amplitude under 5 μV (dotted line) prior to GA in either eye of a patient with abnormal conventional ERG results was considered a true positive for suspected retinal disease.

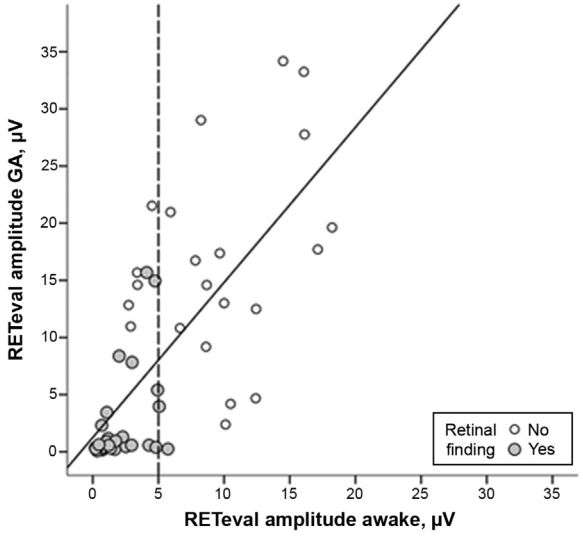

FIG 6. Scatterplot of amplitudes of the RETeval under GA vs prior to GA. A RETeval amplitude under 5 μV (dotted line) prior to GA in either eye of a patient with abnormal conventional ERG results was considered a true positive for suspected retinal disease.

electrodes are 4-5 times smaller than those recorded with contact lens electrodes.[13,14] Despite these differences in magnitude, we found a significant positive correlation for both amplitude and implicit times between the conventional ERG system and the RETeval device, both prior to and under GA. Similarly, Yasuda and colleagues[11] found the amplitudes ($r = 0.66$; $P = 0.008$) and implicit times ($r = 0.89$; $P < 0.001$) of flicker ERGs recorded by the two systems significantly correlated in adults with pupil dilation. Nakamura and colleagues[11] found a significant positive correlation between the amplitudes ($r = 0.576$ [Pearson correlation coefficient]; $P = 0.001$; n = 35) but not the implicit times ($r = -0.065$ [Pearson correlation coefficient]; $P = 0.805$; n = 17) in pediatric and adult patients with a confirmed diagnosis of cone dysfunction. However, in their study the pupils were not dilated for the RETeval ERG but were dilated for the conventional ERG. To deliver constant retinal luminance, the RETeval's pupil-tracking function requires cooperative fixation during the examination. Because we anticipated limited cooperation in our pediatric patients, pupillary dilation was performed in all patients to achieve constant retinal luminance.

General anesthesia lowers ERG amplitude values, attenuating b-wave amplitudes as much as 50%.[6] An unexpected finding of our study is that the RETeval amplitudes were consistently smaller before GA than they were under GA.

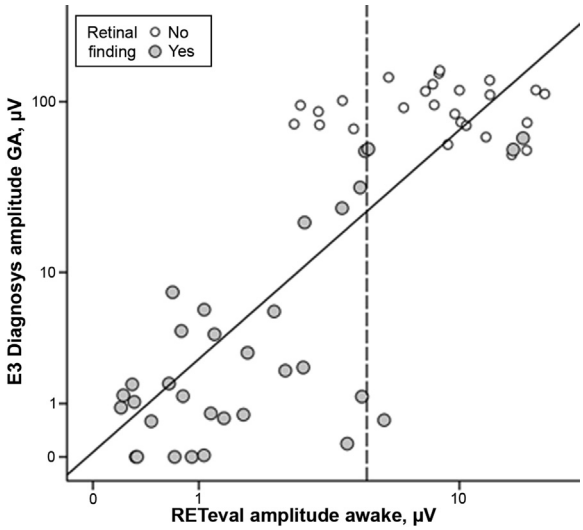

FIG 7. Scatterplot of amplitudes of the conventional ERG vs RETeval prior to GA on log-log scale. The dotted line represents an amplitude value of 5 μV with the RETeval prior to GA.

Our findings are likely explained by the lack of continued fixation in awake pediatric patients, which reduces the measured ERG amplitudes by interfering with the averaging calculations through eye-movement ERG artifacts. We found the amplitude differences between the awake and GA RETeval recordings markedly decreased with increased age, which we attribute to better fixation in older children.

A similar concept regarding the effect of eye-movement ERG artifacts may also apply to patients with nystagmus. Grace and colleagues[12] compared unsedated RETeval recordings of 31 normal patients and 19 patients with nystagmus without a retinal dystrophy and found a statistically significant difference in recordings, with smaller amplitudes ($P = 0.010$) and longer implicit times ($P = 0.016$) in nystagmus patients. Therefore, we can conclude that poor fixation and nystagmus likely affect the averaging calculations of the RETeval device, and these artifacts may occur despite adequate pupillary dilation and good cooperation.

Grace and colleagues[12] established a detection cut-off of amplitude ≤ 5 μV for the RETeval that had a 93% sensitivity and 95% specificity for identifying retinal disorders in children with nystagmus. Applying this cut-off to the amplitude values we obtained with the RETeval in at least 1 eye prior to GA, there was an 85% chance of abnormal conventional ERG results under GA (PPV). If the amplitude was >5 μV in both eyes, there was a 90% chance that the patient would have normal conventional ERG results under GA (NPV). Additionally, if the implicit time is reported as "not measurable" by the RETeval, there should be a high concern for retinal disease, because only 7 of 34 eyes (20%) with an underlying retinal disorder had a measurable implicit time.

There are several limitations in our study. The small number of patients with varied diagnoses make it difficult to generalize the results of our study across retinal conditions. Also, because our study only analyzed children, we cannot say whether these findings apply to adults. Finally, as the RETeval screening test consists of only the 30 Hz cone flicker test, rare patients with predominantly rod dysfunction and preserved cone function, such as those with congenital stationary night blindness, may be missed.

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