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Association of Vitamin A Supplementation With Disease Course in Children With Retinitis Pigmentosa

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Abstract:

Objective: to compare the disease progression in retinitis pigmentosa-affected kids receiving vitamin A supplements to those who do not.

Study design and type: Non-randomised retrospective study

Methodology: The study comprised 55 children receiving vitamin A and 25 not taking vitamin A who had various hereditary forms of typical retinitis pigmentosa. The data analysis was done in December 2022 and the patient examinations took place between June 2016 to May 2022 We used age adjusted dose of vitamin A ≤15 000 IU/d. By using repeated-measures longitudinal regression, we may estimate the mean exponential rates of change of the full-field cone electroretinogram amplitude to 30-Hz flashes without and with confounding variables.

Results: The mean and SD age of the 55 kids in the vitamin A cohort was 9.1± 1.9years, and 38 (69%) of them were boys. The estimated mean rates of change using the unadjusted model were 0.0713 loge units/y (6.9% per year) for the group receiving vitamin A and 0.1419 loge units/y (13.2% per year) for the control cohort (difference, 0.0706 loge units/y; 95% CI for the difference, 0.0149-0.1263 loge units/y; P =.01). The modified model supported the observation that the vitamin A group saw a slower mean rate of decrease (difference, 0.0771 loge-unit per year; 95% CI for the difference, 0.0191-0.1350 loge-unit per year; P =.009).Regarding ocular safety, there were no differences between cohorts in the mean exponential rates of change in visual acuity and visual field area, nor in the incidences of falling to a visual field diameter of 20° or less or a visual acuity of 20/200 or less in at least 1 eye.

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Conclusion: In children with retinitis pigmentosa, taking vitamin A palmitate supplements was linked to a slower reduction of cone electroretinogram amplitude. These results support the use of an age-adjusted dose of vitamin A in the treatment of the majority of children with the typical forms of retinitis pigmentosa, despite the relatively small sample size, retrospective, nonrandomized design, and potential biases.

Keywords:
Vitamin A, Retinitis pigmentosa, paediatric

Introduction:

Using vitamin A and/or vitamin E for 4 to 6 years, we treated 601 persons (aged 18 to 49) with the typical forms of retinitis pigmentosa, and the findings were reported in 1993[1]. As measured by the full-field cone electroretinogram (ERG) to 30-Hz flashes, oral vitamin A palmitate, 15 000 IU/d, appeared to halt the course of retinal degeneration, but oral vitamin E (dl-tocopherol acetate), 400 IU/d, appeared to speed it. Vitamin A showed a substantial benefit with the full-field ERG to 0.5-Hz flashes, but vitamin E showed no significant harm[1]. The Data and Safety Monitoring Committee as a whole came to the conclusion that the majority of adults with retinitis pigmentosa and normal liver function should take vitamin A palmitate and avoid a high dose of vitamin E, despite the fact that 1 member of an independent Data and Safety Monitoring Committee questioned the 2 x 2 factorial design used in the study[2] and 2 members questioned whether the sixth year of follow-up based on a subset should have been included in the analyses[3].It was recommended that pregnant or trying to get pregnant women avoid taking this amount of vitamin A due to a higher risk of birth abnormalities in the unborn child. Neither during the clinical trial nor by the study participants receiving this amount of vitamin A for up to 12 years, any substantial toxic side effects were identified[4]. In 2008, the National Eye Institute issued a press release confirming this recommendation after sending an information alert to thousands of ophthalmologists across North America[5,6]. No formal recommendation could be made for retinitis pigmentosa individuals under the age of 18 because they were left out of the clinical research. But after the research trial's publication, relatives contacted us to inquire if their affected kids might take vitamin A. Pediatricians we consulted recommended an oral dose of 5000 IU/d for children aged 6 to 10 years, 10 000 IU/d for children aged 10 to 15 years, and 15 000 IU/d for children aged 15 years and older, provided the children's blood liver function test results were normal. Parents were instructed to provide their children on vitamin A a balanced diet, refrain from giving them high-dose vitamin E supplements, check their blood liver function annually, and visit our clinic every two years for a follow-up evaluation and potential dose adjustment.A minority of the families whose children were offered treatment did not do

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so on the pediatrician's advice. However, they were also urged to have their kids come back for an evaluation every two years. This led to one group of kids taking vitamin A regularly for a period of time (the vitamin A cohort) and another group not getting vitamin A, including kids who were identified before the clinical trial's publication or who decided against taking vitamin A after publication (control cohort).This study examines if there were any differences between the control cohort's and vitamin A cohort's mean illness courses as measured by the ERG.

Methodology:

The Electroretinography Service frequently informed patients and families that their deidentified health records might be used for upcoming research and obtained their verbal consent. The data analysis was done in December 2022 and the patient examinations took place between June 2016 to May 2022 To measure the effectiveness of vitamin A therapy, we measured the annual rate of change in cone ERG amplitude to 30-Hz full-field white flashes (0.2 cd s/m2). Cone ERG amplitude was substantially linked with patients' vision-related quality of life, giving us the highest power to demonstrate a vitamin A effect in the adult clinical trial using this measure.We regularly capture responses to 30-Hz flashes using band-pass filtering and signal averaging if amplitudes are less than 10 V, allowing quantification of at least.05 V in amplitude[7,8,9]. In accordance with our eligibility criteria for inclusion in a longitudinal study to compare mean rates of cone ERG amplitude decline, a review of our database identified 80 children from 72 families with typical forms of retinitis pigmentosa who had cone ERG amplitudes to 30-Hz flashes recorded on at least 1 subsequent visit spanning at least 3 years in at least 1 eye at their baseline visit. These children had typical forms of retinitis pigmentosa based on clinical examination[7,8,9]. Since we had previously reported a vitamin A treatment benefit by that metric based on kinetic perimetry in the adult clinical trial10, we also gave that comparison some thought. However, that analysis had been restricted to patients with the most reproducible visual field areas on repeated pretreatment testing within 6 weeks, a criterion that was unavailable to us in this study.Additionally, preliminary analyses on children with retinitis pigmentosa affected failed to find, on average, a substantial loss in total visual field area or in visual field area contiguous to the centre throughout follow-up, discrediting its use by us as a marker of disease progression. Because it has not previously demonstrated a vitamin A benefit in adults, decline in visual acuity was disqualified as an outcome measure[1]. However, in order to find ocular proof of supplement safety, we examined longitudinal data on visual field size and visual acuity from these cohorts.

The vitamin A cohort consisted of 55 children: 43 children who started taking supplements after their baseline ERGs but before their first follow-up ERGs, and 12 children who started taking supplements before their baseline ERGs. We discovered

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that children aged 7 to 15 years took 5000 IU/d, a kid aged 14 years took 7500 IU/d, children aged 6 to 15 years took 10,000 IU/d, and children aged 12 to 15 years took 15,000 IU/d. No families with children using vitamin A reported any negative effects from the supplement, despite instances where the age-adjusted recommendation was exceeded. 25 kids from the control cohort did not report taking vitamin A supplements.

Statistical Analysis:

Because cone ERG amplitude was discovered to decline exponentially in patients with retinitis pigmentosa7,11 and a logarithmic transform has been used to quantify full-field cone ERG decline in retinitis pigmentosa by our laboratory[1,7,8,9,11,12,13,14] and another, cone ERG amplitudes were converted to natural logarithms to better normalise their distributions and to fit linear models to time[15,16]. Then, using the eye as the unit of analysis and an unstructured@compound symmetry correlation structure that allows for correlation within the same eye over time, correlation between eyes at one time, and correlation between one eye at one time and the fellow eye at a different time, repeated-measures longitudinal regression was performed. We were able to use pertinent data from all accessible eyes and times thanks to this method.

Model 1 fitted the following equation to the data:

loge amplitude = $b_0 + b_1$(cohort) + b_2(time) + b_3(time)(cohort)

where b_0 represented the y-intercept for cohort = 0 (i.e., the control cohort), b_1 represented the change in intercept for cohort = 1 (i.e., the vitamin A cohort), b_2 represented the coefficient for the effect of time on amplitude (i.e., the slope) for cohort = 0, and b_3 represented the coefficient for the change in the effect of time on amplitude for cohort = 1 (i.e., the vitamin A cohort). As a result, for the cohort of people who took vitamin A, the intercept was equal to $b_0 + b_1$ and the effect of time on amplitude was equal to $b_2 + b_3$.

In order to obtain adjusted results, Model 2 added eye, genetic type, and their cross-products with time in addition to time, vitamin A, and loge visual field area or loge visual acuity for ocular safety studies. We also compared the occurrences of falling to a visual acuity of 20/200 or below in at least one eye across all cohorts at follow-up.Time, loge baseline cone ERG amplitude, and baseline cone ERG implicit time were all mean-centered continuous predictor variables in these models. For analyses without a repeated variable, such as the t test for continuous variables and either the 2 test or Fisher Exact test (where predicted cell frequencies were 5) for proportions, JMP Pro, version 13 (SAS Institute), was used. A 2-sided P value lower than 0.05 was regarded as statistically significant.

Results:

The baseline demographic and cone ERG features of the retinitis pigmentosa-affected

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children are shown in Table 1. With the exception of very little variations in the mean cone ERG implicit (peak) timings and genetic type distributions, the cohorts were equivalent. The vitamin A group had a follow-up period of 5.0 (0.2) years and 3.7 (0.2) visits, while the control cohort had 4.5 (0.4) years and 3.4 (0.2) visits; these two sets of means were comparable. The mean time between follow-up appointments for the vitamin A cohort was 1.35 years, compared to 1.32 years for the control cohort, based on these means.The timing of the first follow-up examination, however, was different across the 2 cohorts: 37 (67%) of those in the vitamin A cohort and only 10 (40%) of those in the control cohort did so within the recommended 2 years.

For the vitamin A cohort (b2 + b3), the estimated mean rates of change with Model 1 were 0.0713 loge-unit per year (6.9% per year) and 0.0706 loge-unit per year (95% CI, 0.0149-0.1263 loge-unit per year; P = 0.01) lower than those for the control cohort (0.1419 loge-unit per year; Table 2, b_2). Plots by cohort and actual (not mean-centered) year based on the anticipated loge amplitude (SE) from the Figure. The fitted line for the vitamin A cohort has a noticeably shallower slope but only a little lower y-intercept (amplitude at year 0) than the fitted line for the control cohort.Regarding supplement ocular safety, an unadjusted analysis showed that mean visual field area increased by 0.0037 loge-unit per year (0.37% per year) in the control cohort and by 0.0241 loge-unit per year (2.4% per year) in the vitamin A cohort (Table 3); the difference was not statistically significant. The 0% (0 of 24 patients) in the control group and 4% (2 of 50 patients) in the vitamin A cohort experienced a fall to a visual field diameter of 20° or less during follow-up; the difference in percentages (4%), however, was not statistically significant (P = 0.45).According to an unadjusted analysis (Table 4), mean visual acuity grew by 0.0012 loge-units annually (0.1% annually) in the control cohort and by 0.0151 loge-units annually (1.5% annually) in the vitamin A cohort. However, the difference in rates was not statistically significant. It was 4.2% (1 of 24 patients) in the control cohort and 5.5% (3 of 55 patients) in the vitamin A cohort for the incidence of falling to a visual acuity of 20/200 or less in at least one eye during follow-up; the difference in percentages (1.3%) was not statistically significant (P = 0.65).

Table 1: Baseline Characteristics[17]

Variables	Treatment group N= 55 (%)	Control Group N= 25 (%)
Mean age (years)	9.1 ± 0.3	9.2 ± 0.3
Gender		
Female	17 (31.9%)	6 (24%)
Male	38 (69%)	19 (76%)
Genetic type		
Unknown	14 (25%)	1 (4%)

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Dominant	10 (18%)	6 (24%)
X-linked	9 (16%)	9 (36%)
Recessive	22 (40%)	9 (36%)
Cone ERG amplitude, geometric mean	6.5	7.2
Cone ERG amplitude, mean (SE), Log_e, μV	1.87 (0.15)	1.98 (0.25)
Cone ERG implicit time, mean (SE), ms	42 (0.6)	39.9 (0.9)

Table 2: Loge Cone ERG Amplitude to 30-Hz Flashes Repeated Measures Longitudinal Regression on Model 1 Variables[17]

Coefficient	Estimate (SE)	Degrees of freedom	95% CI	t-value	Probability >|**t**|
b_3	0.0706 (0.0283)	393	0.0149 to 0.1263	2.49	0.013
b_2	-0.1419 (0.0244)	393	-0.1898 to -0.0940	-5.82	<0.001
b_1	0.0850 (0.2176)	78	-0.3483 to 0.5183	0.39	0.70
b_0	1.5874 (0.1816)	78	1.2258 to 1.9490	8.74	<0.001

Table 3: Loge Visual Field Repeated-Measures Longitudinal Regression on Model 1 Variables[17]

Coefficient	Estimate (SE)	Degrees of freedom	t-value	95% CI	Probability >|**t**|
b_3	0.0204 (0.0283)	424	0.72	-0.0353 to 0.0760	0.47
b_2	0.0037 (0.0241)	424	0.15	-0.0436 to 0.0511	0.88
b_1	0.1282 (0.1196)	72	1.07	-0.1102 to 0.3667	0.29
b_0	9.0416 (0.0987)	72	91.61	8.8449 to 9.2383	<0.001

Table 4: Loge Visual Acuity Repeated-Measures Longitudinal Regression on Model 1 Variables[17]

Coefficient	Estimate (SE)	Degrees of freedom	t-value	95% CI	Probability >|**t**|
b_3	0.0139 (0.0168)	321	0.82	-0.0192 to 0.0469	0.41

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b_2	0.0012 (0.0146)	321	0.08	-0.0274 to 0.0299	0.93
b_1	0.0875 (0.0698)	67	1.25	-0.0517 to 0.2268	0.21
b_0	-0.5929 (0.0576)	67	-10.29	-0.7079 to -0.4779	<0.001

Discussion:

The findings indicate that during follow-up, the cone ERG amplitude declined at a statistically significant slower exponential rate in the vitamin A group than in the control cohort. The analysis adjusting for covariates confirmed that the slowing with vitamin A was at least as large as that with the unadjusted model. The unadjusted analysis allowed estimation of the mean rates of decline to have been 13.2% per year in the control cohort and 6.9% per year in the vitamin A cohort. According to these projections, the vitamin A cohort fell to half baseline amplitude on average in 9.7 years compared to 4.9 years for the control cohort, a difference of over 2 times.It is possible that a vitamin A supplement for patients with retinitis pigmentosa is more effective in children because the size of this vitamin A benefit in children was greater than that from the adult clinical trial (i.e., 10% per year for the trace cohort vs. 8.3% per year for the vitamin A cohort based on the same amplitude eligibility criteria)[1]. The proportion of children whose visual field diameter decreased to 20° or less or whose visual acuity decreased to 20/200 or less in at least one eye during follow-up, as well as the mean rates of change of visual field or visual acuity, did not reveal any safety concerns related to vitamin A supplementation.

Notable are two ancillary results. First, a bigger response in youngsters should not rule out a quick future illness course because the exponential rate of cone ERG amplitude loss increased with rising baseline amplitude, increasing by a mean 3.6% per year for a 2.7-fold increase in baseline amplitude. Second, regardless of baseline amplitude, the rate of cone ERG amplitude loss increased with increasing baseline cone ERG implicit time, increasing by a mean 1.1% for every 1-ms increase in baseline implicit time. This study expands on a related observation made in people with retinitis pigmentosa with dominant RHO mutations, where only 16 children (20%) had a dominantly inherited illness[18]. If cone ERG implicit time is a biomarker for the rate of disease progression in retinitis pigmentosa in general, it could be used to select patients to shorten the length of clinical trials when cone ERG amplitude decline is the outcome measure and to help predict the prognosis of any given patient in the absence of intervention. Unfortunately, rates of full-field cone ERG amplitude decline unique to children with various genetic variants of typical retinitis pigmentosa have not previously been reported to support

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these further findings, to the best of our knowledge.

Conclusion:

We recommend that children with typical retinitis pigmentosa and normal liver function consider oral supplementation with an age-appropriate dose of vitamin A palmitate under a pediatrician's supervision in an effort to slow the loss of cone function in light of the positive ERG results, the evidence of supplement safety, and potential biases from the relatively small-sample, retrospective, nonrandomized study design. Children with a longer cone ERG implicit time who are at a higher risk for aggressive disease may find this guidance to be especially helpful. The effectiveness of other therapeutic modalities (such as gene therapy) that rely on the quantity and condition of residual cone photoreceptors may be increased by such supplementation, which may also promote retention of visual field,[19]mobility, and vision-related quality of life[1].

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