Improvement of central retinal sensitivity six months after topical isopropyl unoprostone in patients with retinitis pigmentosa

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Aims: Isopropyl unoprostone (IU), a maxi-K channel activator, is used topically to treat glaucoma, and has been reported to have neuroprotective effects on retinal neurons in vitro and in vivo. The purpose of this non-comparative pilot study was to determine whether topical IU will alter the sensitivity of the central retina in patients with retinitis pigmentosa (RP). Settings and Design: Non-comparative pilot study. Materials and Methods: IU was given topically twice a day for 6 months to both eyes of 30 patients with typical RP. The visual acuity was measured with a Japanese Snellen chart, and the mean retinal sensitivities were obtained by fundus-related microperimetry (MP-1). The mean deviation (MD) of the visual field was determined with a Humphrey field analyzer (HFA). All measurements were made before and 6 months after the treatment. Statistical Analysis Used: Wilcoxon and the Mann-Whitney U tests (SPSS, SPSS Inc., Chicago, IL.). Results: After the treatment, the mean retinal sensitivity within the central 2° and 10° improved significantly from 12.3 ± 4.8 dB to 14.7 ± 5.5 dB (P = 0.001) and from 9.1 ± 5.4 dB to 11.0 ± 6.2 dB (P = 0.001), respectively. Conclusions: These short-term results suggest topical IU can improve the central retinal sensitivity in RP patients. It will be necessary to examine longer treatment periods in a controlled study to determine the effectiveness of topical IU in RP patients.

Key words: Humphrey field analyzer, isopropyl unoprostone, microperimetry, retinitis pigmentosa

Retinitis pigmentosa (RP) is the name given to a group of inherited retinal degenerative diseases, characterized by night blindness and progressive decrease of peripheral vision. At more advanced stages, the central vision is also reduced.[1,2] The worldwide prevalence of retinitis pigmentosa is about 1 in 4000 for a total of more than 1 million affected individuals.[1,2] Typically, RP begins with a degeneration of the rods followed by progressive and irreversible death of the cones, which leads to blindness.[1,2] Because the mutations damage the rods initially, the preservation of cones is an important goal for preserving vision in RP patients.

With the exception of vitamin A nutritional supplementation,[1,3] no treatment has been shown to be effective for RP. In a recent phase 1 clinical trial, patients with severe RP received ciliary neurotrophic factor (CNTF), delivered within encapsulated cells that were implanted intracocularly. Patients who received the CNTF had some improvement in vision.[4] More recently, two institutions used RPE65 gene replacement and reported that there was an improvement of visual function in patients with Leber congenital amaurosis, a severe autosomal recessive retinal dystrophy.[5,6] Although cell therapy or gene replacement therapy may be the ultimate method to rescue photoreceptor cells in patients with RP, it is still reasonable to test drugs with known neuroprotective properties and good safety profile on RP patients.

In rats, an impaired choroidal circulation is probably involved in the mechanism of the delayed cone cell death after light toxicity.[7] A reduction of the choroidal blood flow has been reported in patients with RP[8] and thus improving the choroidal circulation may help preserve cone photoreceptors in RP patients. In addition, an increase in the plasma level of endothein-1 has been reported in RP patients.[9] It is known that endothein-1 is involved in the contraction of the smooth muscles of blood vessels.

Isopropyl unoprostone (IU; Rescula®, R-tech Ueno, Tokyo, Japan) is a chemically synthesized docosanoid (22-carbon basic skeleton), which is being used to treat eyes with glaucoma or ocular hypertension. In Japan, 0.12% IU was approved for use in 1994, and 0.15% IU was approved in the USA in 2001. IU was initially developed to lower an intraocular pressure, but later, studies showed that topical 0.12% IU increased retinal and choroidal blood flow in glaucoma patients in Japan.[10,11] In addition, topical IU was shown to partially block the endothelin-1-induced vasoconstriction of the human choroidal vessels, leading to an increase in choroidal blood flow.[12] In rats, an intravitreal injection of IU was shown to protect photoreceptors from light damage,[13] and this neuroprotective power of IU may be related to its ability to increase retinal and choroidal blood flow.

The purpose of this study was to determine whether topical IU will improve the central retinal function of RP patients. To accomplish this, we measured the central retinal sensitivities with an automatic fundus-related perimeter in 30 RP patients before and after a twice-daily application of IU.

Materials and Methods
A prospective, non-comparative pilot study to test the effectiveness of IU on central retinal sensitivities in eyes with RP was conducted at our hospital from January to October in 2007.
The experimental protocol was approved by the Institutional Review Board of our hospital. After explaining the procedures to be used and the possible side effects, an informed consent was obtained from 30 consecutive patients with typical RP who were initially examined between January to April of 2007. Their mean age was 52.9 ± 12.8 years with a range from 23 to 73 years. There were 16 men and 14 women.

The diagnosis of RP was made from the clinical history, funduscopic appearance, visual field tests, fluorescein angiography, and the results of full-field electoretinograms (ERGs) recorded with the International Society of Clinical Electrophysiology of Vision (ISCEV) parameters. Patients with systemic syndromes associated with an RP-like fundus appearance, and those with cataracts or vitreous opacities, which may affect the optical coherence tomography (OCT) examinations, were excluded. None of the patients had cystoid macular edema determined by the OCT, and none of the patient had diabetes mellitus, ocular inflammatory diseases, primary retinal vascular diseases, or glaucoma. Eyes that had undergone intraocular surgery were also excluded.

Only 1 of the eyes from each patient was analyzed; the data from the right eye was used. This was a pilot study and not a comparable one, thus we did not have a control group.

IU 0.12% was given twice a day, at 2 drops per dose, separated by 5 minutes to both eyes for 6 months.

The best-corrected visual acuity (BCVA), retinal sensitivity measured by microperimetry, and the visual fields measured with the Humphrey field analyzer were recorded before and 6 months after the IU treatment. The primary endpoint of this study was the changes of sensitivity of the central retina of the 2°, evaluated through MP-1, and the secondary endpoint was the changes of sensitivity of the central retina of the 10°, evaluated through MP-1, MD through HFA 10-2, and the BCVA. The side effects of IU were also monitored at each visit, and the compliance was monitored orally at the same time.

The BCVA was measured with a standard Japanese Snellen chart in decimal units. For VA measurement, the refraction was performed using a standardized refraction protocol. The decimal acuities were then converted into the logarithm of the minimum angle of resolution (logMAR) for statistical evaluation. The BCVA was better than 0.6 (0.22 logMAR) in all RP patients studied.

Microperimetric measurements were made with the pupils dilated with 0.5% tropicamide eye drops on all subjects. Patients were not dark-adapted before the measurement, and the contralateral eye was patched during the testing. Patients were allowed to practice the measurement before the first test to eliminate learning effect. The right eye was always tested first in each patient.

The measurements were made with an automatic fundus-related perimeter, the MP-1 (Microperimeter; Nidek Technologies, Padova, Italy). With this system, the fundus is imaged in real time on a video monitor with an infrared fundus camera (1392 × 1038-pixel resolution; 45° field of view). The fixation target and stimuli were displayed on a liquid crystal color monitor whose positions were completely controlled by dedicated software. The background illumination was set at 1.27 cd/m², and the stimulus intensity could be changed in 0.1 log unit steps from 0 to 20 dB where 0 dB represents the brightest luminance of 127 cd/m².

The following parameters were used on the MP-1: A 3° red single cross fixation target; a white background of 1.27 cd/m²; Goldman III stimulus size, projection time of 200 ms; a rectangular 3 × 3° test grid with 24 stimulus locations covering the central 10° centered on the fovea [Fig. 1]. A 4-2 double-staircase method was used. The stimulus was projected exactly onto a predefined retinal position by an automatic eye-tracker that compensated for eye movements. This allowed a correct matching between the expected stimulus position on the retina and an actual projected position. The mean retinal sensitivity within the central 2° was determined from the central 4 points, and the mean retinal sensitivity within the central 10° was determined from all 24 points.

The position and intensity of the light stimuli were randomly presented during the examination as in standard static perimetry. A test stimulus was projected every 60 seconds onto the optic nerve head to check for a false-positive answer. To allow for better clinical correlation between microperimetric data and retinal details, the functional results were superimposed on a color digital retinograph, acquired by a charge-coupled device color camera (1392 × 1038 pixels, xenon flash) For the 6 month follow-up examination, a new refractive error was entered into the MPI software for each patient, and the follow-up system was used to examine the same retinal locations. The Humphrey field analyzer (HFA; Carl Zeiss Meditec, Inc, Dublin, California, USA) was used with the central 10-2 full threshold program to obtain another measure of macular function. Reliability indices were also recorded. Patients’ pupils were not dilated for the HFA examinations.

The significance of the differences between the pre-treatment and post-treatment data was assessed by Wilcoxon and the Mann-Whitney U tests (SPSS, SPSS Inc., Chicago, IL). All of the data are presented as means ± standard deviations (SDs). A P value < 0.05 was considered to be statistically significant.

Results

The age, gender, BCVA in logMAR, MD values from HFA, and the mean retinal sensitivity obtained by the MP-1 are shown for the 30 cases in Table 1. The mean retinal sensitivity within the central 2° before IU was 12.3 ± 4.8 dB, and it was 14.7 ± 5.5 dB after 6 months. For the central 10°, the mean retinal sensitivity was 9.1 ± 5.4 dB before the IU and 11.0 ± 6.2 dB after 6 months. For both sizes, the improvements in the sensitivities after IU were significant in MP-1 (P = 0.001 for 2°, P = 0.001 for 10°) [Table 2]. There were no side effects of IU use.

Within the central 2°, the retinal sensitivity in 17 of the 30 (57%) eyes improved by ≥ 2.0 dB after IU, and 11 of the 30 (37%) eyes improved by ≥ 4.0 dB [Fig. 2]. The central retinal sensitivities in 3 of the 30 (10%) eyes decreased by ≥ 2.0 dB after the IU.

For the central 10°, 12 of the 30 (40%) eyes improved by ≥ 2.0 dB after IU, and 5 (17%) eyes improved by ≥ 4.0 dB after the IU [Fig. 3]. None of the eyes decreased by ≥ 2.0 dB after the treatment. 7 of 8 eyes whose pre-IU retinal sensitivity was < 6.0 dB for the 10° did not show an improvement of the mean retinal sensitivity.
Table 1: Visual acuity, retinal sensitivity by MP-1, and mean deviation by HFA before and after topical unoprostone treatment

| Case | R/L | age/sex | BCVA  | MP-1 2° | MP-1 10° | HFA 10-2 |
|------|-----|---------|-------|---------|----------|----------|
|      |     |         | Pre   | Post    | Pre      | Post     |
|      |     |         |       |         |          |          |
| 1    | R   | 47M     | -0.08 | 0.00    | 9        | 12       |
| 2    | R   | 42F     | 0.00  | 0.00    | 15.5     | 20       |
| 3    | R   | 63M     | 0.00  | 0.05    | 6.5      | 6.5      |
| 4    | R   | 60F     | -0.08 | 0.00    | 18       | 19.5     |
| 5    | R   | 38M     | -0.18 | -0.08   | 14.5     | 18       |
| 6    | R   | 63M     | -0.08 | -0.08   | 6.5      | 9.5      |
| 7    | R   | 50F     | -0.18 | -0.18   | 18       | 13.5     |
| 8    | R   | 33F     | 0.00  | 0.00    | 9        | 18       |
| 9    | R   | 60M     | -0.18 | -0.18   | 11       | 20       |
| 10   | R   | 59F     | 0.00  | 0.05    | 19.5     | 20       |
| 11   | R   | 63M     | -0.08 | -0.08   | 13.5     | 18       |
| 12   | R   | 53F     | 0.00  | 0.00    | 20       | 17.5     |
| 13   | R   | 52M     | -0.18 | -0.18   | 12.5     | 18.5     |
| 14   | R   | 50F     | 0.10  | 0.16    | 13       | 18       |
| 15   | R   | 37M     | 0.00  | 0.00    | 13.5     | 9.5      |
| 16   | R   | 55M     | 0.10  | 0.05    | 10.5     | 9.5      |
| 17   | R   | 57M     | 0.10  | 0.10    | 11       | 10.5     |
| 18   | R   | 62F     | -0.08 | -0.08   | 14       | 18       |
| 19   | R   | 72M     | 0.00  | 0.16    | 8.5      | 15       |
| 20   | R   | 66F     | 0.00  | 0.10    | 12       | 17.5     |
| 21   | R   | 73M     | 0.05  | 0.16    | 15.5     | 20       |
| 22   | R   | 59F     | 0.05  | 0.22    | 14       | 13.5     |
| 23   | R   | 61M     | 0.00  | 0.05    | 5        | 3.5      |
| 24   | R   | 51M     | 0.00  | 0.00    | 4        | 5        |
| 25   | R   | 64F     | 0.05  | 0.16    | 15.5     | 16       |
| 26   | R   | 60F     | -0.08 | 0.05    | 11       | 15.5     |
| 27   | R   | 41M     | -0.08 | 0.00    | 16.5     | 20       |
| 28   | R   | 23F     | 0.00  | 0.10    | 14.5     | 17       |
| 29   | R   | 51F     | -0.18 | 0.00    | 18       | 20       |
| 30   | R   | 23M     | 0.22  | 0.22    | 0        | 0.5      |

BCVA: Best-corrected visual acuity in log MAR units, MP-1 2° = Retinal sensitivity in dB within the central 2° measured with MP-1, MP-1 10° = Retinal sensitivity in dB within the central 10° measured with MP-1, HFA 10-2 = Mean deviation in dB by Humphrey Field Analyzer (program 10-2).

Table 2: Summary of changes in visual acuity, retinal sensitivity by MP1, and mean deviation by HFA

|                  | Baseline | 6 months | P    |
|------------------|----------|----------|------|
| VA               | -0.026 ± 0.097 | 0.026 ± 0.109 | 0.001 |
| MP-1 2°          | 12.3 ± 4.8 | 14.7 ± 5.5 | 0.0007 |
| MP-1 10°         | 9.1 ± 5.4  | 11.0 ± 6.2 | 0.000003 |
| HFA 10-2         | -13.9 ± 9.8 | -13.8 ± 10.0 | 0.71 |

BCVA: Best-corrected visual acuity in logMAR units, MP-1 2° = Retinal sensitivity in dB within the central 2° measured with MP-1, MP-1 10° = Retinal sensitivity in dB within the central 10° measured with MP-1, HFA 10-2 = Mean deviation in dB by Humphrey Field Analyzer (program 10-2).

Figure 1: Photograph of the fundus of a RP patient showing the MP-1 test grid composed of 24 stimulus locations within the central 10°.

3 eyes (Cases No. 23, 24, and 30) with <6 dB retinal sensitivity as determined by MP-1 at the baseline for both 2° and 10° did not show significant improvements after IU application. ($P = 0.84$ for 2°, $P = 0.69$ for 10°).
The changes in the MD obtained from the HFA 10-2 program before and after IU treatment are shown in Fig. 4. The average of the MD was $-13.9 \pm 9.8$ dB before the IU application and $-13.8 \pm 10.0$ dB 6 months after the IU ($P = 0.71$). The reliability indices were <33% for all measurements.

The average BCVA was $-0.026 \pm 0.097$ logMAR before and $0.026 \pm 0.109$ logMAR 6 months after the IU. This reduction in the BCVA is significant ($P = 0.001$).

**Discussion**

The results of this non-comparable pilot study showed that topical IU significantly improved the retinal sensitivities within the central 2° and 10° at 6 months. However, the MD values obtained by HFA 10-2 did not change significantly. This difference may come from that MP-1 evaluated the central 10° in diameter of the central retina while the HFA tested the central 20° in diameter. Cone cells are located within 2° more. As MP-1 has auto-tracking and follow-up systems that allowed the examiner to test the retinal sensitivity in the same retinal area before and after the treatment. MP-1 was able to detect slight changes in the retinal sensitivity after treatment compared with conventional HFA, which does not have this tracking system.

Topical administration of IU has been shown to significantly increase the blood flow in the optic nerve head, retinal microcirculation, and choroidal circulation in animals and humans. An instillation of 3 or 4 drops of 0.12% IU led to a partial dilation of the endothelin 1-induced vasoconstriction in the human choroid. These finding indicated that topical IU can penetrate into the eye after topical administration, and alter the blood flow in the retina and choroid.

3 eyes (Cases No. 23, 24, and 30) with <6 dB retinal sensitivity as determined by MP-1 at the baseline for both 2° and 10° did not show significant improvements after IU. ($P = 0.84$ for 2°, $P = 0.69$ for 10°) Thus, we believe that IU can be effective for RP patients whose central retinal sensitivity is ≥ 6 dB before the application of IU. At this stage, the damage of the cones may be reversible.

The major limitation of this study is that we did not have a control group, and it is not possible to eliminate learning effects for MP-1 measurements completely, even though the learning effect may be minimal because the interval between the first and last tests was 6 months. The next comparative controlled study using the fellow eye as control would be necessary to confirm reproducibility of sensitivity measurements to evaluate the real effects of IU.

In conclusion, our short-term results suggest that topical application of IU can improve the central retinal sensitivity of the 2° or the 10° in RP patients. Our findings also show that the auto-tracking and follow-up systems of the fundus-related perimeter of the MP-1 are essential to detect slight changes of retinal sensitivity. Further studies are needed with a placebo control group, a larger sample size and longer follow-up periods.

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