Therapeutic Effect of Diode Laser Photodynamic Therapy with ICG Dye in ARMD: A Case Report

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Purpose: To evaluate the diode laser photodynamic therapy efficacy on choroidal neovascularization (CNV) in the treatment of three patients with age-related macular degeneration (ARMD).
Methods: The authors selected three patients with ARMD whose vision has decreased due to CNV, and applied diode laser treatment after injecting an indocyanine green (ICG) solution. The patients were followed for at least three months after treatment, and examinations included evaluating vision changes and possible leakage on fluorescein angiography (FAG).
Results: The final vision of two patients improved by more than one line on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart after at least three months of follow-up. However, the final vision of the third patient decreased by one line on ETDRS chart. FAG was done in all patients, and in two of the patients, there was no evidence of leakage at the laser-applied site. In the other patient, there was evidence of minimal leakage, with the area of leakage decreasing by more than fifty percent. Side effects of ICG were not found during or after the photodynamic therapy sessions.
Conclusions: The photodynamic usage of ICG treatment of CNV in patients with ARMD, was effective in preventing or improving the visual outcome. Compared to the widely used verteporfin, ICG is more stable and is more cost effective. The authors therefore came to a conclusion that ICG can be very useful in the treatment of CNV. However, further studies are necessary.
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Choroidal neovascularization (CNV) arises underneath the retinal pigment epithelial (RPE) layer, and is characterized by hemorrhage, retinal edema, subretinal edema, fibrosis, and eventually loss of vision. Among various causes of CNV, age-related macular degeneration (ARMD) is an important cause of blindness in the elderly population in the Western hemisphere. The incidence of ARMD is also increasing in Korea, due tothe growing elderly population.

Laser photocoagulation has been recommended as a conventional treatment modality. However, in cases with subfoveal CNV, foveal damage during photocoagulation was inevitable, causing decrease in vision, central scotoma, and a high incidence of recurrence. Compared to conventional photocoagulation, photodynamic therapy (PDT) with verteporfin was able to induce regression of neovascularization while minimizing the retinal damage.

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However, one of the side-effects of verteporfin is photosensitivity, and when patients were exposed to light after the photodynamic therapy with verteporfin, they complained of skin rashes or pruritis. The patients were unable to go outside for 48 hours after receiving PDT with verteporfin. Furthermore, when there is a leakage of the dye during the injection, the patient may develop skin necrosis, and rarely, the patient may experience back pain. Due to the treatment's high cost, many patients have given up on the treatment altogether.

In contrast, the indocyanine green (ICG) dye is very stable, has no photosensitivity, is inexpensive, and has been used in the fluorescein angiography for years. Because there have been reports of the effective outcome of treating CNV patients with ICG dye, the authors selected three CNV patients with ARMD and treated these patients by photodynamic therapy with ICG dye. The authors then analyzed the clinical results of these patients, examining the photodynamic effectiveness of ICG dye (and its superiority to verteporfin in stability and cost) in the treatment of CNV in patients with ARMD.

Case Report

Among the patients who were diagnosed with CNV due to ARMD and underwent PDT from April of 2003 to the present, the authors selected three patients (three eyes total) for retrospective analysis. With each patient, visual acuity with and without correction was measured, and the anterior segment of the patients' eyes were examined with a slit-lamp. A dilated retinal exam was also done with contact lenses and an indirect ophthalmoscope, and FAG was done in order to identify CNV. The patients were asked about allergic reactions to iodine, shellfish, and crustaceans, all of which were negative.

PDT was conducted by intravenously injecting ICG dye with concentration of 50 mg/2.5 cc (Diagnogree, Cheil pharmaceutical co., Japan). In order to allow the dye to reach the eye without dilution, 5 cc of normal saline was injected. Then, the diode laser with a wavelength of 805 nm was mounted on the slit-lamp and applied to the retina with the spot size of 3000 μm for 90 seconds. The authors calibrated the power of the laser between 575 mW and 1500 mW. The patients were then followed-up for one month after the PDT, and then three months after that.

Afterwards, the authors examined the patients once every three months and measured the best-corrected visual acuity with the ETDRS chart, conducted a dilated retinal examination, and performed FAG. With the natural progression of CNV in mind, the authors defined stabilization of visual acuity after PDT as the visual acuity decreasing by less than two lines on ETDRS chart. The authors defined progress of visual acuity as the patient obtaining more than one line of improvement on ETDRS chart.

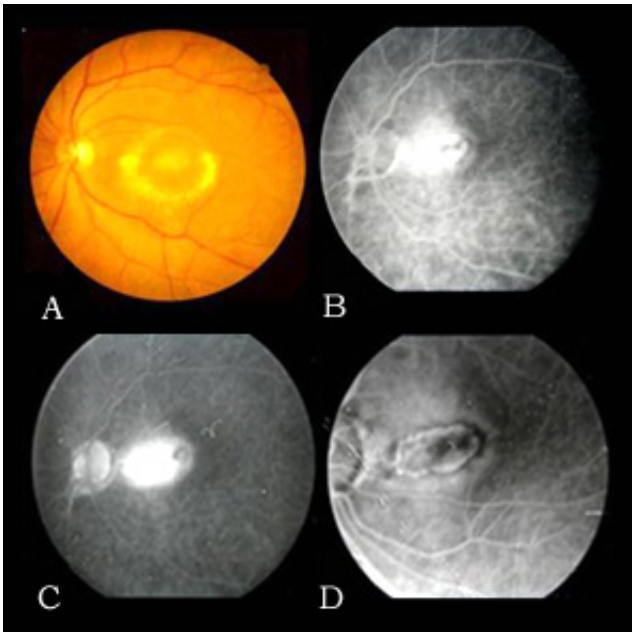

Fig. 1. Color photograph and angiographic findings of CNV due to ARMD. (A) The color photograph shows RPE atrophy and hypertrophy in the macular area of the left eye. (B) Early phase of FAG before treatment shows classic CNV in the subfoveal area, which is smaller than one disc diameter. (C) Late phase of FAG before treatment shows hyperfluorescence from leakage on CNV area. (D) Three months after treatment, no leakage was noted on FAG or hyperfluorescence due to RPE atrophy.

When there was no leakage compared to the previous findings identified by FAG, the patient was said to have "no leakage". The patient was said to have "minimal leakage" when the area of leakage was no more than fifty percent of the original leakage, and "moderate leakage" when the area was more than fifty percent. Finally, when the leakage exceeded the original area of the lesion, the progression" label was given to the patient's leakage, and the analysis was completed.

Case 1

A 74-year-old male patient reported a decrease in visual acuity in his left eye that began six months before his initial visit to the hospital. His vision with or without correction on his left eye was 20/2000, and his vision with and without correction on his right eye was 20/25 and 20/50, respectively.

The patient had no past history of hypertension or diabetes, and the anterior segment of his eye appeared normal. Dilated retinal examination showed atrophy as well as hypertrophy of the retinal pigment epithelial (RPE) layer in the left foveal region. The patient also had an exudate. FAG showed classic CNV the size of an optic disc, located in the subfoveal region. The lesion showed hyperfluorescence at first; the area of hyperfluorescence increased towards the end of the FAG due to leakage (Fig. 1A-C).

ICG dye was injected intravenously with a concentration of 50 mg/2.5 cc. Two minutes later, an additional 5 cc of normal saline was injected. The diode laser was then applied to the patient's retina with the spot size of 3000 μm for 90 seconds. The authors calibrated the power of laser at 1000 mW. There were no allergic or adverse effects due to ICG dye during or after the therapy session.

The patient was followed-up for three months, and his best-corrected visual acuity one month after the treatment increased by one line to 20/800. However, his visual acuity showed no additional improvement three months after the treatment. The authors looked at his FAG taken three months after the treatment, and found "no leakage" on both occasions (Fig. 1D).

During his final visit, the authors found atrophy of the retinal pigment epithelial layer, and there was no evidence of RPE detachment. However, the patient continued to complain of metamorphopsia.

Case 2

A 66-year-old female patient complained of metamorphopsia beginning three months before her initial visit to the hospital. Her visual acuity with or without correction was

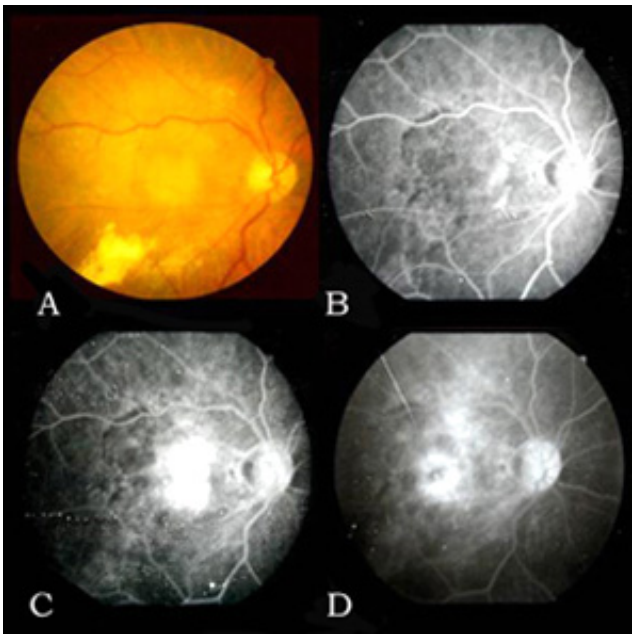

Fig. 2. Color photograph and angiographic findings of CNV due to ARMD. (A) The color photograph shows RPE atrophy and hypertrophy, soft drusen, and exudate in the macular area of the right eye. (B) Early phase of FAG before treatment shows occult CNV in the subfoveal area, which is smaller than one disc diameter. (C) Late phase of FAG before treatment shows hyperfluorescence from leakage in the CNV-involved area. (D) Nine months after treatment, minimal leakage was noted on FAG.

20/400 in her right eye and 20/25 in her left eye. The patient had no past history of hypertension or diabetes, and the anterior segment of her eyes appeared normal.

Dilated retinal examination showed atrophy as well as hypertrophy of right foveal region, and the patient also had a soft drusen and exudate. The patient's FAG showed occult CNV the size of an optic disc located in the subfoveal region, and an area of hyperfluorescence increased towards the end of the FAG due to leakage (Fig. 2A-C).

ICG dye was injected intravenously, and a diode laser was applied to the patient's retina with the spot size of 3000 μm for 90 seconds. The authors calibrated the power of the laser at 1500 mW.

The patient was followed up for nine months, and her best-corrected visual acuity improved by more than two lines to 20/250. The degree of metamorphopsia also decreased. According to FAG taken nine months after the treatment, the patient showed "minimal leakage", involving an area no more than 50% of the original leakage (Fig. 2D). Dilated retinal examination done in her final visit showed atrophic changes in the retinal epithelial layer, and there was no evidence of retinal hemorrhage or RPE detachment.

The patient did not experience any allergic or adverse reactions to the ICG dye during or after the treatment session.

Case 3

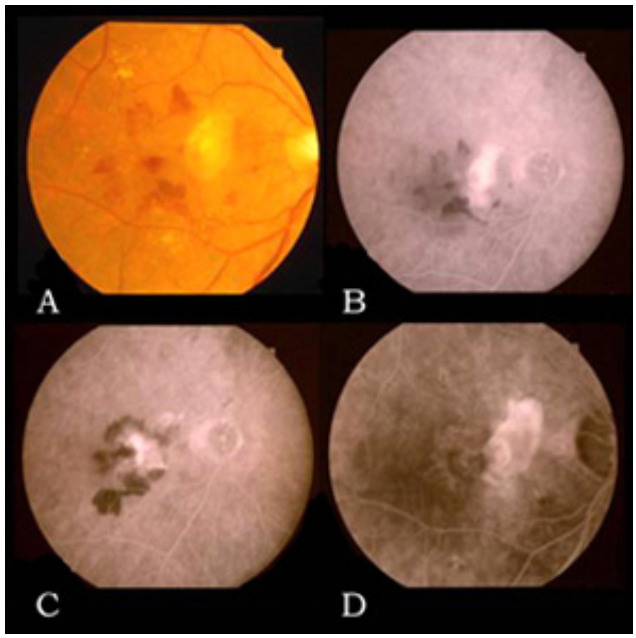

Fig. 3. Color photograph and angiographic findings of CNV due to ARMD. (A) The color photograph shows RPE atrophy and hypertrophy, soft drusen, and exudate in the macular area of the right eye. A small amount of hemorrhage is also observed around the macular area. (B) Early phase of FAG before treatment shows a hyperfluorescent lesion on the nasal side of the macula due to RPE atrophy. (C) Late phase of FAG before treatment shows hyperfluorescence from leakage of occult CNV in the subfoveal area, which is smaller than one disc diameter. (D) Nine months after treatment, no leakage was noted on FAG.

A 56-year-old male patient reported decreased visual acuity and metamorphopsia beginning six months prior to the initial visit to the hospital. His visual acuity with or without correction was 20/2000 in his right eye, and 20/25 in his left eye. The patient had no past history of hypertension or diabetes, and the anterior segment of his eyes appeared normal.

Dilated retinal examination showed atrophy as well as hypertrophy of the retinal epithelial layer in his right macular region. There was no evidence of a soft drusen or small areas of retinal hemorrhage in the macula. FAG revealed a hyperfluorescent area located in the nasal macular region due to atrophy of the RPE layer, and a subfoveal occult CNV the size of an optic disc showed increase in the area of hyperfluorescence towards the end of the FAG due to leakage (Fig. 3A-C).

ICG dye with a concentration of 50 mg/5 cc was injected intravenously, and a diode laser was applied to the patient's retina with the spot size of 3000 μm for 90 seconds. The power of laser was calibrated at 575 mW.

The patient was then followed up for nine months, and his final best-corrected visual acuity of the right eye worsened by one line on the chart at 20/1333. Metamorphopsia also remained. His final FAG findings showed "no leakage" (Fig. 3D). Dilated retinal examination done in his final visit

revealed atrophy of the RPE layer, and there was no evidence of retinal hemorrhage or RPE detachment.

The patient also reported no allergic or adverse reactions to ICG dye during or after the treatment session.

Discussion

CNV occurs underneath the retina or RPE layer, and leakage or hemorrhage because of neovascularization, ischemia, or fibrosis can damage the retina, decreasing visual acuity.[1,2]

Causative factors of CNV include ARMD, ocular histoplasmosis, high myopia, and other idiopathic causes.[3] Among these causes, ARMD is a degenerative disease of the macula which occurs in patients in their fifties and older. It is characterized by soft drusen, hyper- or hypopigmentation of the RPE layer, detachment of the sensory retina, retinal hemorrhage, geographic atrophy of the RPE, and CNV or fibrotic changes of the retina. In the Western hemisphere, ARMD has become a main cause of blindness in the elderly population over 60 years of age. Its prevalence is also increasing in Korea.[4] It can be classified into atrophic or exudative degeneration, and most cases of severe visual loss occur in patients with exudative ARMD with accompanying CNV.

Many different treatment modalities have been tried in order to cure CNV, including pharmaceutical or radiological therapy, subfoveal surgery, or laser photocoagulation.[5] Different pharmaceutical treatments have also been tried (e.g., thalidomide, interferon α -2a, and anti-VEGF) but they were generally ineffective; research is still ongoing.[6] Radiological therapy was known to reduce proliferation of vascular endothelial cells ex vivo, thereby preventing proliferation of neovascular vessels in vivo. However, there have been contrasting reports regarding maintenance or amelioration of visual acuity after treatment.[7] Subfoveal surgery has been tried in patients who have severe subfoveal hemorrhage and CNV, in patients with large CNV where laser photocoagulation cannot be done, and in patients with CNV which has ambiguous margin. However, there have been reports of serious complications such as the development of cataract, the recurrence of CNV, and retinal detachment. Finally, laser photocoagulation can decrease the incidence of severe visual loss, but in cases of subfoveal CNV, hyperthermia caused by laser can also damage healthy sensory retina. Cases are limited where laser treatment can be effective, and recurrence after five years is more than 50%.[8] Thus, in patients with subfoveal CNV, there are no satisfactory treatments.

However, while studying agents that can selectively work with CNV, PDT (which employs photosensitive agents) has been developed. PDT has been clinically proven in the treatment against cancer, and research has been conducted in order to prove its efficacy in the treatment against CNV. Schmidt-Erfurth and Hasan reported that photosensitive agents can be absorbed into neovascular vessels, and they successfully demonstrated photothrombosis in an experiment involving animals.[9] Among photosensitive agents, the second-generation agent verteporfin has been proven to selectively induce CNV regression, and because the agent can also prevent laser-induced hyperthermia, it has become a widely used agent during photodynamic therapy.[10,11]

Verteporfin can bind with tumors that have multiple low-density lipoprotein (LDL) receptors and can also selectively unite with neovascular vessels, thereby giving out singlet oxygen and free radical. As a result, new vessels may become clogged due to photothrombosis.[12] PDT, which employs verteporfin, has been proven in the treatment of CNV due to ARMD after a random prospective study of the treatment of AMD with photodynamic therapy (TAP) was published, and this study included two years of clinical results.[13] In the phase I and II study that examined the safety of verteporfin, short-term visual outcome and effectiveness was exemplified by FAG: hyperfluorescent leakage decrease-dafter a short period of time (one to four weeks), and normal retinal vessels or visual acuity remained intact. The study also showed that the leakage coming out of CNV recurred after 12 weeks.[14,15]

However, after injecting verteporfin, patients reported photosensitive symptoms such as rash, eczema, facial edema and flushing. The patients were instructed not to expose their skin, eyes, or other organs directly to sunlight, artificial tanning machines, bright halogen light, or other sources of bright indoor lighting. Furthermore, when verteporfin is injected along with other photosensitizing agents such as tetracycline, sulfonamides, phenothiazines, sulfonylurea, hypoglycemic agents, thiazide diuretics, and griseofulvin, a photo-allergic reaction may be amplified. Additionally, when verteporfin is used with free radical oxygen, anticoagulants, agents which constrict vessels, thromboxane A2, dimethyl sulfoxide, betacarotene, ethanol, formate, or mannitol, its therapeutic effect decreased markedly. When the patient is taking calcium channel blockers or polymyxin-B or is receiving ultraviolet therapy, the therapeutic effects of verteporfin will also decrease because these agents decrease selectivity to neovasculature. In order to overcome these defects of verteporfin, some studies started to employ ICG dye in PDT because the dye does not cause photosensitivity.[16]

ICG is an anionic tricarbocyanine lavender-hued dye, and, ever since it was introduced by an American Fox in 1957, it has been widely used in liver and heart function tests. It has also been used in FAG of the retina and choroid for more than thirty years.[17] After the dye is injected intravenously, it combines with blood proteins and spreads throughout the body. Because it is absorbed by the liver, it does not pass freely through the gastrointestinal tract or through the kidneys. Twenty minutes after injection, 97% of the dye is digested by the liver and excreted through the gallbladder. This makes the dye a very stable agent when measuring liver and circulatory function, because one can freely determine

the residual amount in the blood or its loss thereof, and the amount of blood flow into the liver. With the exception of patients who are allergic to iodine (which is included in the ICG), the dye is safe to use, and it poses no toxicity to skin.

When ICG is diluted into a solution, its maximum wavelength changes from 780 nm to 805 nm after it combines with blood proteins, and such a property can be used in PDT. PDT consists of two parts: the injection of a photosensitive agent and the application of a non-thermal laser to the sensitized tissue. After the injection of ICG, the dye unites with blood proteins (e.g. LDL, albumin, etc.) and among these proteins, LDL increases in number within vascular endothelial cells of rapidly proliferating cells (such as choroidal neovascular vessels). The expression of LDL receptor also increases accordingly. Thus, the combined unit of ICG and LDL accumulates within CNV, and when the non-thermal laser is applied to the site, this unit changes from a ground singlet form to an excited triplet form. ICG makes a photochemical reaction with this triplet form, giving rise to free radicals or transforming it into singlet oxygen. These singlet oxygen and free radicals can damage the endothelial cells, expose the basement membrane of vessels, and activate the platelets, thereby making the platelets combine and coagulate. These activated platelets can secrete vasoactive mediators, causing thrombosis and constriction of vessels, thereby clogging the new vessels.

Among non-thermal lasers employed in the PDT, the ICG enhanced diode laser photocoagulation was first used by Puliafito et al. for the treatment of CNV.[18] The wavelength of the diode laser varies between 780 and 840 nm, and the laser has maximum output of 2~3 W, making photocoagulation of retina possible. Also, maximum absorption wavelength of ICG dye is identical to that of the laser at 805 nm, enabling the laser to penetrate deep into the tissue.[19] Furthermore, the wavelength is within that of the infra-red light, making penetration through cornea and lens easy, and since the laser is not absorbed by other pigments such as xanthophylls, flavoprotein, and glutathion peroxidase, it can be very useful in the treatment of subfoveal lesions.[20]

In one study published Obana et al., which examined the effectiveness of ICG dye and diode laser, Obana reported the therapeutic effect in regression of macular CNV to be up to 92%.[21]

While Obana conducted his clinical study with humans, the authors of this study previously took pigmented rats, and, after creating artificial CNV in the retina of rats, injected ICG dye, applied a diode laser, and observed the regression of CNV. The authors found that the therapeutic effect of such treatment to be up to 85%.[22]

When the authors analyzed the clinical results of this study, one month after the treatment, there was visual improvement of 0.3 lines. Three months after the treatment, there was another 0.3 lines of improvement. The visual acuity did not continue to improve six months and nine months after the treatment, and the overall average increase in visual acuity was 0.2 lines. As FAG data were analyzed, two eyes had "no leakage" while one eye had "minimal leakage.

In the TAP study that studied the effectiveness of PDT with verteporfin, improvement of visual acuity was defined as improving more than a line on ETDRS chart after taking into account the natural progression of CNV. One can argue that the authors' study failed to prove that the therapy with ICG failed to bring about improvements in visual acuity. However, the visual acuity can be defined as stable when there is deterioration of no more than two lines on the chart, and the authors concluded that the therapy with ICG at least can stabilize the progression of CNV. Also, when the authors looked at the changes in the amount of leakage on FAG, "moderate leakage" (greater than 50% of the original leakage) or "progression" did not occur in all patients, further exemplifying the CNV-stabilizing effect of PDT with ICG. The location of CNV in all three cases was either directly subfoveal or near the area, and because there was no massive hemorrhage, the final visual outcome of PDT could have been good.

This study does have its limitations that, unlike the TAP study that studied the effectiveness of PDT with verteporfin, the authors did not attempt to treat the patient when there was further leakage on FAG, and the patient pool was rather small. Also, in one patient's eye, only a short period of follow-up (three months) was possible, making a direct comparison of ICG to verteporfin difficult.

However, compared to the TAP study, the visual acuity stabilizing effect of ICG was comparable to that of verteporfin, making the dye useful in the treatment of ARMD with CNV. Furthermore, compared to verteporfin, ICG is safer because it does not give rise to any allergic or adverse reactions to light, and is cost effective.

Thus, the authors concluded that in patients with decreased visual acuity due to ARMD with concomitant CNV, PDT with ICG can be employed with expectation of improving the visual acuity at a relatively cheaper cost.

Further studies are necessary in order to compare both the short- and long-term visual outcomes of PDT with ICG dye, and also to study whether such treatment can be employed with other causes of CNV such as pathologic myopia, ocular histoplasmosis, and idiopathic CNV.

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