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Subthreshold Nanosecond Laser, from Trials to Real-Life Clinical Practice: A Cohort Study

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Contents

ABBREVIATIONS

AMD = age-related macular degeneration, GA = Geographic atrophy
BCVA = best-corrected visual acuity, logMAR =Logarithm of the Minimum Angle of Resolution
BM = Bruch's membrane, CNV = Choroidal neovascularization
CI = confidence interval, OCT = Optical coherence tomography
ECM = extracellular matrix
IAMD = intermediate age-related macular degeneration
MMP = matrix metalloproteinase
nAMD = neovascular age-related macular degeneration
LEAD = Laser Intervention in Early Stages of Age-Related Macular Degeneration
MMI = multimodal imaging, HRT = Heidelberg Engineering Retinal Tomography
RPD = reticular pseudodrusen
SNL = subthreshold nanosecond laser
2RT= retinal rejuvenation therapy.

Zusammenfassung

Ziel

Diese Studie zielt darauf ab, die klinische Entwicklung von Symptomen und Komplikationen bei Patienten mit früher und mittelschwerer AMD (altersbedingte Makuladegeneration) zu bewerten, die mit einer unterschwelligen Nanosekunden-Lasertherapie (SNL) behandelt werden. Die SNL-Therapie ist eine nicht-invasive, schmerzfreie Behandlungsmethode mit einem frequenzverdoppelten Nanosekunden-Pulslaser mit diskontinuierlicher Strahlenergieverteilung.

Methoden

An einer einzigen Institution wurde eine Kohort-studie durchgeführt. Zwischen 2015 und 2018 wurden 438 Patienten mit früher und mittlerer AMD (Alter 55-80) identifiziert. 160 Patienten wurden nach der Ausschlusskriterien identifiziert. Die Patienten, die der SNL-Therapie zustimmten, waren 64 Patienten, die anderen Patienten lehnten die SNL-Therapie ab und wurden als Kontrollgruppe eingeschlossen. Die Patienten mit Pseudodrusen wurden identifiziert und ausgeschlossen. Die primären Endpunkte waren die Verringerung der Anzahl und Drusenfläche als Umkehrung früher klinischer Indikatoren für AMD. Die sekundären Endpunkte waren die Veränderung der mittleren Sehschärfe nach dem 6. Monat und das Fortschreiten zu einer fortgeschrittenen altersbedingten Makuladegeneration (AMD) im behandelten Auge. Um teilnahmeberechtigt zu sein, sollten die Patienten zuvor keine anderen Augenerkrankungen haben, die die interessierenden Ergebnisse beeinflussen könnten, wie z. B. diabetische Retinopathie, Katarakt, schweres Glaukom oder Behandlung während der Studie.

Ergebnisse

Es wurde eine Umkehrung früher klinischer Anzeichen von AMD dokumentiert, die sich in einer Verringerung der Anzahl und Größe der Drusen zeigten (jeweils $p < 0,001$). Innerhalb des 6-monatigen Follow-up war die Progressionsrate der Drusengröße und -anzahl in der SNL-Gruppe signifikant niedriger (26 %) als in der Kontrollgruppe (69 %; $p < 0,001$). Keine Verbesserung der Sehschärfe (LogMar) wurde in der SNL-Gruppe im Vergleich zur Nicht-SNL-Gruppe dokumentiert (jeweils p 0,59).

Fazit

Diese Studie hebt die SNL-Therapie als mögliche Therapieoption hervor, um die frühen klinischen Anzeichen von AMD umzukehren. Die vorliegende Studie liefert neue Hinweise darauf, dass Patienten mit früher und mittlerer AMD von der minimal-invasiven SNL-Therapie profitieren könnten

Summary

Goal

This study aims to evaluate the clinical development of symptoms and complications in patients with early and moderate AMD (age-related macular degeneration) treated with subliminal nanosecond laser therapy (SNL). SNL therapy is a non-invasive, painless treatment method with a frequency-doubled nanosecond pulsed laser with discontinuous beam energy distribution.

Methods

A cohort study was conducted at a single institution. Between 2015 and 2018, 438 patients with early and moderate AMD (age 55-80) were identified. 160 patients were identified according to the exclusion criteria. The patients who consented to the SNL therapy were 64 patients, the other patients refused the SNL therapy and were included as a control group. The patients with pseudrusen were identified and excluded.The primary endpoints were the reduction in the drusen area as a reversal of early clinical indicators of AMD. Secondary endpoints were change in mean visual acuity after 6 months and progression to advanced age-related macular degeneration (AMD) in the treated eye. To be eligible, patients should not previously have any other eye conditions that could affect the outcomes of interest, such as diabetic retinopathy, cataract, severe glaucoma, or treatment during the study.

Results

A reversal of early clinical signs of AMD has been documented, which manifested itself in a reduction in the number and size of Druze ($p < 0.001$ each). Within the 6-month follow-up, the progression rate of Druze size and number was significantly lower in the SNL group (26%) than in the control group (69%; $p < 0.001$). No improvement in visual acuity (LogMar) has been documented in the SNL group compared to the non-SNL group (p 0.59 each).

Result

A reversal of early clinical indicators of AMD represented in drusen reduction in number and size were documented. ($p< 0.001$, respectively). Within the 6-month follow-up, the rate of progression in drusen size and number was significantly lower in the SNL group (26%) than in the control group (69%; $p<0.001$). No improvement in the visual acuity LogMar was documented in the SNL-group comparing to the non-SNL group (p 0.59, respectively).

Conclusion

This study highlights SNL-Therapy as a possible therapy option to reverse the early clinical indicators of AMD. The present study provides new evidence that patients with early and intermediate AMD could benefit from the minimal invasive SNL therapy.

1. Introduction

Age-related macular generation (AMD) is a common cause of irreversible loss of vision in individuals over 65 years of age in industrialized countries. Some 200 people in 2020 were affected by AMD worldwide (1, 2). Approximately 9% cases of blindness are due to this disease. The prevalence of AMD has recently increased remarkably like in Germany the number of people with early AMD increased from 5.7 million in 2002 to 7 million in 2017- an increase of 23% in the last 15 years. Patients with later stage of AMD, neo-vascular AMD is 1.4 times more common than the geographical atrophy (3-6, see table 2). This rise in the prevalence of figures may be due not only to aging of the population but also to better ascertainment through improved diagnosis. The data in table 1 support the strong impact of demographics on the prevalence of AMD can be seen in the rise of age-adjusted prevalence of the disease from 24% in people aged between 64-74 years to more than 44% in people aged 70-95 (7-8).

Intravitreal anti-VEGF therapy has helped to reduce the loss of vision from neovasucular AMD, however there is no therapy which is proven to treat geographic atrophy (GA). There lies a need for effective therapies to decrease the progression risk from early to late stage AMD. The AMD pathogens is not completely understood and is considered to be multifactorial (9). The sign of early AMD is a progressive focal accumulation of abnormal extracellular debris which lies between the retinal pigment epithelium (RPE) and Bruch's membrane (BM) also known as soft drusen, whereas the diffuse accumulation occurs within the BM which results in reduced transmembrane transport (10). AMD's clinical classification is: early AMD with medium soft drusen and no pigmentation abnormalities; intermediate AMD with large soft drusen or medium soft drusen with pigment abnormalities and late AMD (11). In early and intermediate AMD, the soft drusen load increases over time. Soft drusen load is a major biomarker of risk of progression to late AMD. Immensely large soft drusen also known as drusenoid pigment epithelial detachment (DPED) are at high risk spectrum (12). The pigmentary changes, hyperreflective foci (HRF) and hyporeflective drusen cores (HDC) are high risk SD-OCT biomarkers. Though they are not a part of AMD classification, reticular pseudodrusen, focal accumulations of debris in the subretinal space is now identified as a phenotype with high risk of progression. Moreover, RPD, with a number of distinct genetic and systematic links has been suggested as a separate disease pathway to late AMD (13).

The continuous wave (CW) laser is absorbed by RPE and is transformed to thermal energy which results in the destruction of RPE with collateral damage to the neighboring neuro-retina and choroid. Laser induced retinal damage is considered to produce therapeutic impact for a number of retinal diseases. Observation about CW laser leads to soft drusen regression in AMD, a number of studies have investigated if it decreases the rate of progression to late AMD. Cochrane review of pooled data from 11 RCTs stated that though CW laser leads to the regression of drusen it does not impact the progression to late disease neither increases the risk of nAMD or vision loss. CW laser leads to substantial destruction of RPE and outer retina which may result in scotomata and laser-induced choroidal neovascular membrane. Subthreshold lasers means delivery of decreased laser energy that no retinal changes are seen at the application time. The goal is to attain targeted RPE energy absorption sufficient for cell damage with minimized collateral damage to the adjacent tissues. The therapeutic impact is

considered to come from consequent RPE cell repair processes (14). The 3-ns Nanosecond pulsed laser has same features as conventional 532-nm CW photocoagulation lasers but the duration of the pulse selectively modulates the pigmented tissues and minimizes the thermal damage to the retinal neurons . There lies a major limitation in the existing literature about the clinical development of symptoms and complications of early and intermediate AMD patients who are treated with SNL therapy (15). Therefore, a comprehensive and better understanding is required to advise patients related to prognosis, evaluating new treatment options and giving interventions based on evidence. Therefore, the objective of the current study is to assess the clinical development of symptoms and complications in patients with early and intermediate AMD treated with SNL therapy and to evaluate whether the treatment could alter the morphological symptoms or signs of early stages of AMD.

1.1 Objectives

The objective of our study is to evaluate the clinical development of symptoms and complications in participants with early and intermediate AMD treated with SNL-Therapy and to assess if this treatment could alter the morphological signs of the early stages of AMD.

2. Material and Methodology

2.1 Study Design

This study was conducted in Cologne- Germany and was designed as a cohort study and performed in accordance with good clinical practice (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) E6), the Declaration of Helsinki II. All patients were fully informed in detail about the therapy and the possible complications, and written informed consent was obtained from all patients before initiation of the treatment. According to national medical regulations for observational single-center studies, the Ethics Committee of the University of Cologne ruled that approval was not required for this study. All tenets of the Declaration of Helsinki and applicable national regulations and laws were observed.

2.2 Participation and Eligibility

In the current study, a natural history cohort was included from a private ophthalmology practice for comparison of drusen resolution. Figure 1 shows the total numbers of subjects 438 patients with AMD diagnosis before the exclusion criteria and loss to follow-up. 160 patients with AMD are identified after applying the exclusion criteria. The remaining 141 patients with AMD without pseudodrusen are derived, of which 64 are in the treatment group, and 77 are in the control group.

The patients were divided according to the inclusion and exclusion criteria into two arms (SNL and control groups). When visual acuity and the fundus status were the same, the eyes were randomized and assigned as a study eye. Clinical status of the fellow eye ranged from presence of any signs of the early stages of AMD through intermediate stage AMD. Eyes were not eligible if they had retinal thickening from any other cause or had undergone any ocular surgery prior 6 months. Eyes were randomized to either SNL or the control group, the patients had to decide to choose or reject the therapy, those who rejected the

SNL-Therapy were assigned as a control group Each participant was involved in the study for a minimum of 6 months, and the total duration of the study was 12 months, including review and data analysis. The data were entered electronically by a trained clinician. Postoperative examinations occurred at 1 day and 6 months. An early review, postoperatively, were carried out to monitor possible adverse effects on the RPE and Bruch membrane. Fundus color photography was performed at 6 months. All participants underwent a standardized examination ophthalmic examination, clinical eye examination using slit-lamp biomicroscopy of the anterior and posterior segments, color fundus photography, auto-fluorescence images (Spectralis HRA+OCT; Heidelberg Engineering, Germany) infra-red images (Spectralis HRA+OCT) and optical coherence tomography (OCT) scans of the macula (Spectralis HRA+OCT and Cirrus HD-OCT; Carl Zeiss Meditec, California, USA) were performed pre-treatment and after 6 months follow-up and interview regarding history and current symptoms of eye diseases, medical history, and medication. When needed, an additional examination in the retinal clinic, including fluorescein angiography, was undertaken to verify the presence of CNV. Perimetry tests were conducted, before any imaging or clinical examination was performed.

2.3 Quantification Parameters and Distance Calibration

The SNL laser delivers single pulses at a wavelength of 532nm with a pulse duration of 3 nanoseconds. Laser spot size is fixed at 400μm diameter, with a fine speckle energy distribution beam profile applied coaxially through a slit-lamp microscope and 1:1 macular contact lens (Area Centralis Volk Ophthalmic Inc). Each patient received, in a single session, 20-24 using an ultra-low energy laser spots (3-ns, 2RT laser; Ellex, Adelaide, Australia) were targeted between the superior and inferior macular arcades, with energy levels of a spot individually titrated. The spots should be titrated to be under the visual threshold for retinal change (range 0.15–0.45 mJ). The laser was coupled to a slit lamp and used a digital interface to record the number of pulses, energy/pulse, and total treatment energy. If the initial pulse energy resulted in a visible lesion, the pulse energy was reduced until no lesion was visible. Typically, no more than three trial exposures were required. The energy were modified according to the individual findings depending on corneal, lens or vitreous opacities, and also retinal pigmentation variations. In previous studies, serious ocular adverse events were defined as evidence of retinal bleeding at the time of treatment, loss of visual acuity from the initial visit (two or more logMAR lines), development of RPE rips, RPE detachments, geographic atrophy, or cataract. Given the short pulse duration of this laser, special attention was directed at the integrity of the Bruch membrane. Fundoscopy, OCT were examined to identify possible adverse effects of laser such as choroidal neovascularization and pathologic RPE changes. Drusen area was determined by using gold standard methods of estimating drusen area based upon color fundus photographs using image J program (16). The proportions of laser-treated eyes with reduced drusen area were compared with that observed in the natural history control group. Any eyes that had progressed to late disease (geographic atrophy, choroidal neovascularization) were excluded from further analysis of drusen area (17). Subsequently all images, including the FAF and OCT images, from baseline to 6 months, were graded for the presence of GA or CNV. Geographic atrophy was defined as sharply delineated areas of RPE hypopigmentation, larger than 175 lm with visible choroidal vessels in its base and was either non-central GA where the atrophy was located outside the central field of 1000 lm diameter and no

t considered advance AMD, or central GA, which was one of the two forms of advanced AMD. Choroidal neovascularization included serious detachment of the sensory retina, or hemorrhagic or serious pigment epithelial detachment. Any suggestion of CNV was confirmed by fluorescein angiography. A disc form scar was referred as a well-defined stable scar. Change in pigment was not used as a marker of disease severity as the laser treatment occasionally created pigmentary changes at the site of the treatment.

2.4 Statistical Analysis and Data Collection

All data organization was carried out in Microsoft Office Excel 2010, whereas statistical analysis was performed with Statistical Package of Social Sciences version 19.0 software. VAs were recorded and converted from Snellen to Log MAR for statistical analysis [18]. At the visit, all patients had a complete ophthalmological check, including best-corrected visual acuity, slit lamp examination, intraocular pressure measurement (Goldman applanation tonometry) and macular evaluation with optical coherence tomography. Visual acuity and macular evaluation was repeated at 6-month follow-up visit. The results were checked for normal distribution using histogram and Shapiro-Wilk test. Since the data were not normally distributed, the Friedman's ANOVA Test was used for the repeated measures in 6 months period for the two groups. The 2-tailed significance Wilcoxon sign test was used for related samples. Thus, the test could be made for significant differences in the values between two different time points. A Student's T-Test was carried out on logMAR BCVA, Drusen size and number at baseline and 6 months to investigate a difference in the outcome measures and to calculate the P value and 95% confidence interval. A P value of 0.05 or less was considered significant. The rate of progression and the relative risk were calculated by measuring the relationship between two binary quantities (The use of SNL therapy and the incidence of progression) using chi-square test.

3. Results

As can be seen from the figure 2, there was a steady decrease in the number and size of drusen in the first 6 months, The drusen number in the control group at baseline was 37.3 ± 21.1 (range, 6-88), and after 6 months follow up the number was 43.6 ± 24.5 (range, 9-90). This increase in drusen number was significant ($p<0.001$, 95% CI= 36.9 – 50.3). In the SNL group, the drusen number at baseline was 29.4 ± 19.2 (range, 3-74), and after 6 months the drusen number was reduced to 24.7 ± 14.8 (range, 1-29). This reduction of the drusen number was statistically significant ($p<0.001$, 95% CI= 20.6-28.7, Figure 3). The drusen size (µm) in the control group at baseline was 40.6 ± 20.3 (range, 12.4-93.1), and after 6 months 49.3 ± 28.4 (range, 11-116.5) showing a significant increase ($p<0.001$, 95% CI = 39.4-59.2). In the SNL group, the drusen size (µm) at baseline was 59.9 ± 44.8 (range, 7.1-171) and after 6 months 48.9 ± 34.4 (range, 4.8-125.8), revealing a significant reduction ($p <0.001$, 95% CI = 36.9-61, Figure 4). The best corrected visual acuity (LogMar) in the control group was 0.2 ± 0.21 (range, 0.0-0.7) at baseline and 0.2 ± 0.19 (range, 0.0-0.7) after 6 months. This difference did not reach statistical difference ($p = 0.59$, 95 % CI = 0.1 – 0.3). The best corrected visual acuity (LogMar) in the SNL group was 0.18±0.12 (range, 0.0-4.0) at baseline and 0.15±0.12 (range, 0.0-0.4) after 6 months. This difference did not reach statistical significance ($p = 0.63$, 95% CI = 0.1 – 0.2). Within six months follow-up, the rate of drusen progression was 26% in the SNL group and 69% in the control group. This difference was significant ($p<0.001$). None of the patients showed any severe complications such as uveitis, retinal detachment, retinal bleeding or vision loss.

4. Discussion

The aim of this study was to find out the functional and the morphological effect of using nanosecond laser in early and intermediate AMD patients in terms of safety and efficacy. To do so, the study examined the clinical development of early and intermediate AMD patients who were treated with SNL therapy and then the outcomes of it were compared with the ones which were not treated with SNL therapy. The study found that SNL therapy was effective in bringing improvement by reducing the biomarkers of AMD progression. Drusen remained the classical marker for the progression of AMD although other markers in serum and urine were also identified [19].

The study had its limitation such as small sample size and this was due to strict exclusion criteria of the study. This strict exclusion criteria led to an accurate check of the accurate effect of SNL therapy. Another limitation of the current study was that the patient population follow-up was not carried out on a regular basis. The current study documented a structural improvement without a significant visual improvement, therefore it can be hypothesize that the different outcome of patients treated with SNL therapy could be because of the complexity of the cases, the extent of initial retinal changes and the deposition of extracellular deposits between RPE and Bruch's or damage to the photoreceptors could play an important role in the efficiency of the treatment. The findings of the current study are in line with the findings of another studies in which drusen regression followed by prophylactic laser treatment was observed [20]. Another study showed that the SNL treatment might play a role in slowing down the progression for those without coexistent RPD [21]. This form of RPD has been recognized as a late age related macular degeneration form. [22, 23] therefore, it can be hypothesize that macular morphology can be improved if an early treatment is carried out after the diagnosis of AMD. That is why an early intervention may help to maintain a better macular morphological appearance as well as decrease the cost and challenges that may lead to the progression of late AMD.

A way to achieve it is by going on regular routine eye check before the appearance of complication. The use of nutritional supplement for curing early AMD has shown limited success [24, 25] and this raised the need for a novel and innovative approach to treatment that could help to reverse the early clinical signs of AMD. A thorough evaluation of clinical influence and the possible long-term negative events of SNL therapy in controlled clinical studies, prospective, large are necessary even if the existing literature showed no evidence of any serious negative impact to the therapy in the energy used for under the visual threshold for the retinal change. Moreover, further research is necessary to show its potential in decreasing the risk of transformation into advanced AMD.

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6. Figures

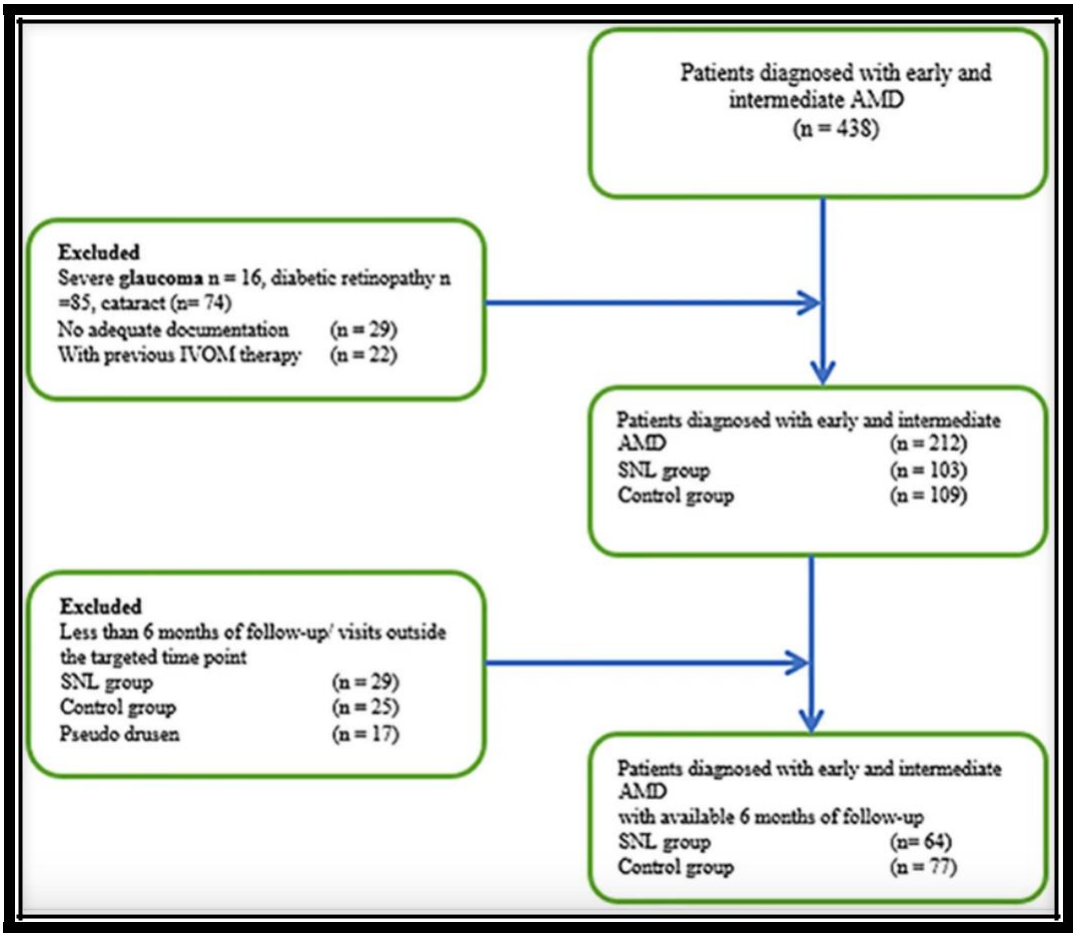

Figure 1 Patient inclusion and exclusion in two arms (SNL and control groups) (26).

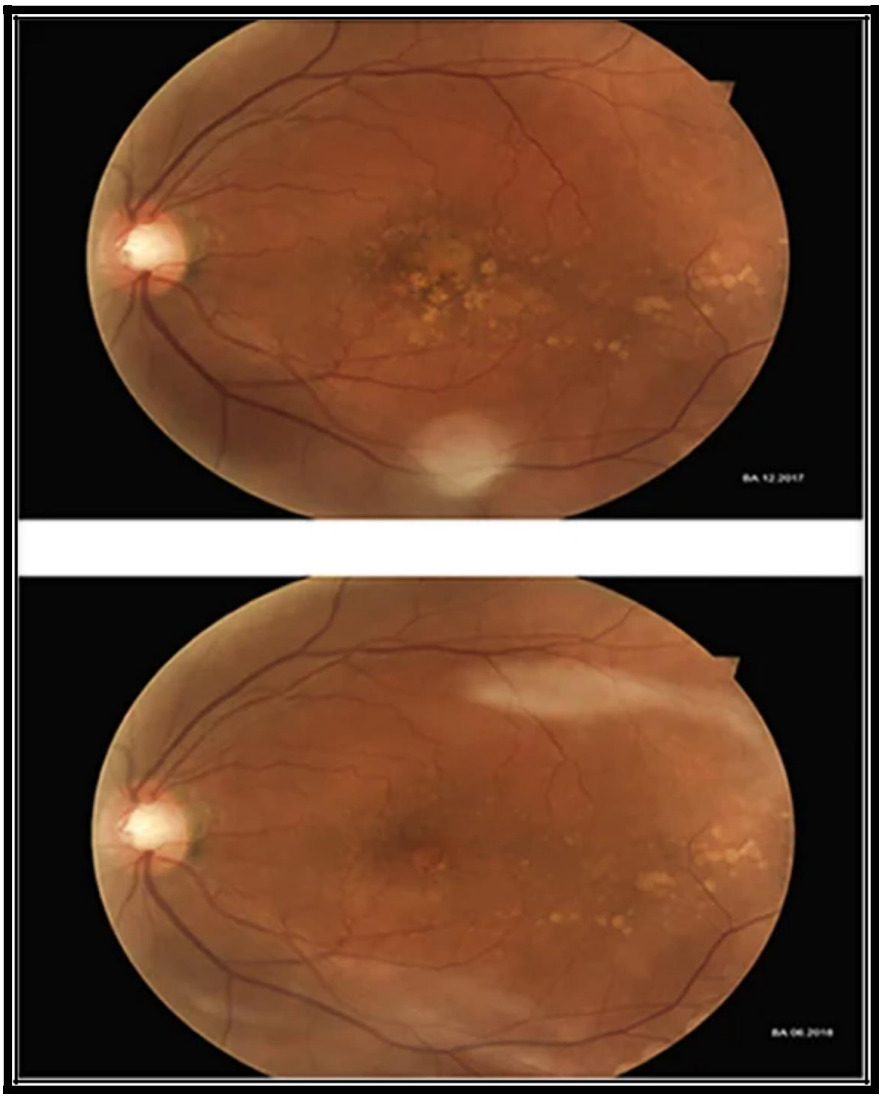

Figure 2 Fundus photograph showing the macular morphological features 6 months after using SNL therapy (26).

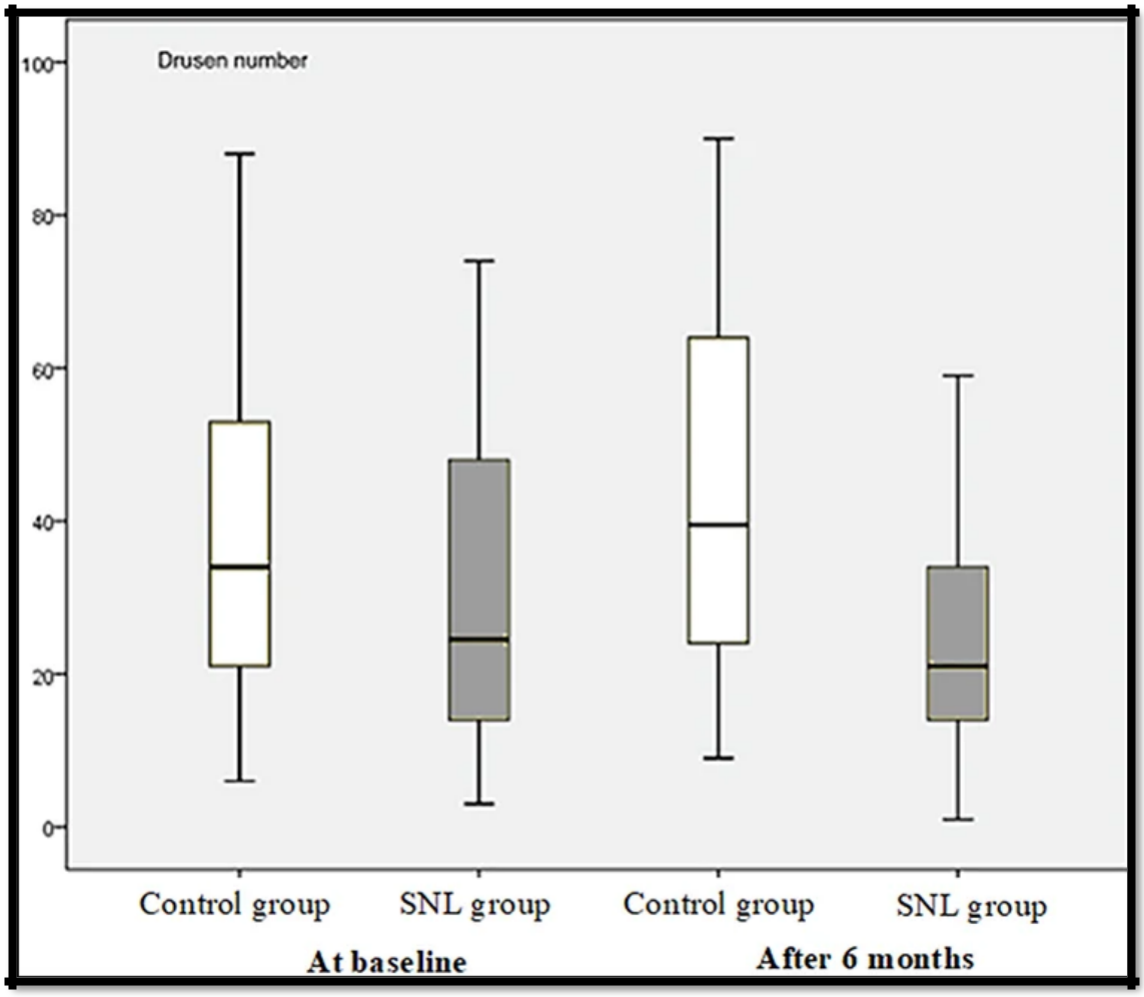

Figure 3 The drusen number in the control group at baseline was 37.3±21.1 (range=82.6–88), and after 6 months follow-up, the number was 43.6±24.5 (range=81.9–90, p <0.001, 95% CI=36.9–50.3). In the SNL group, the drusen number at baseline was 29.4±19.2 (range=71.3–74), and after 6 months it was 24.7±14.8 (range=58.1–59, p<0.001, 95% CI=20.6–28.7) (26).

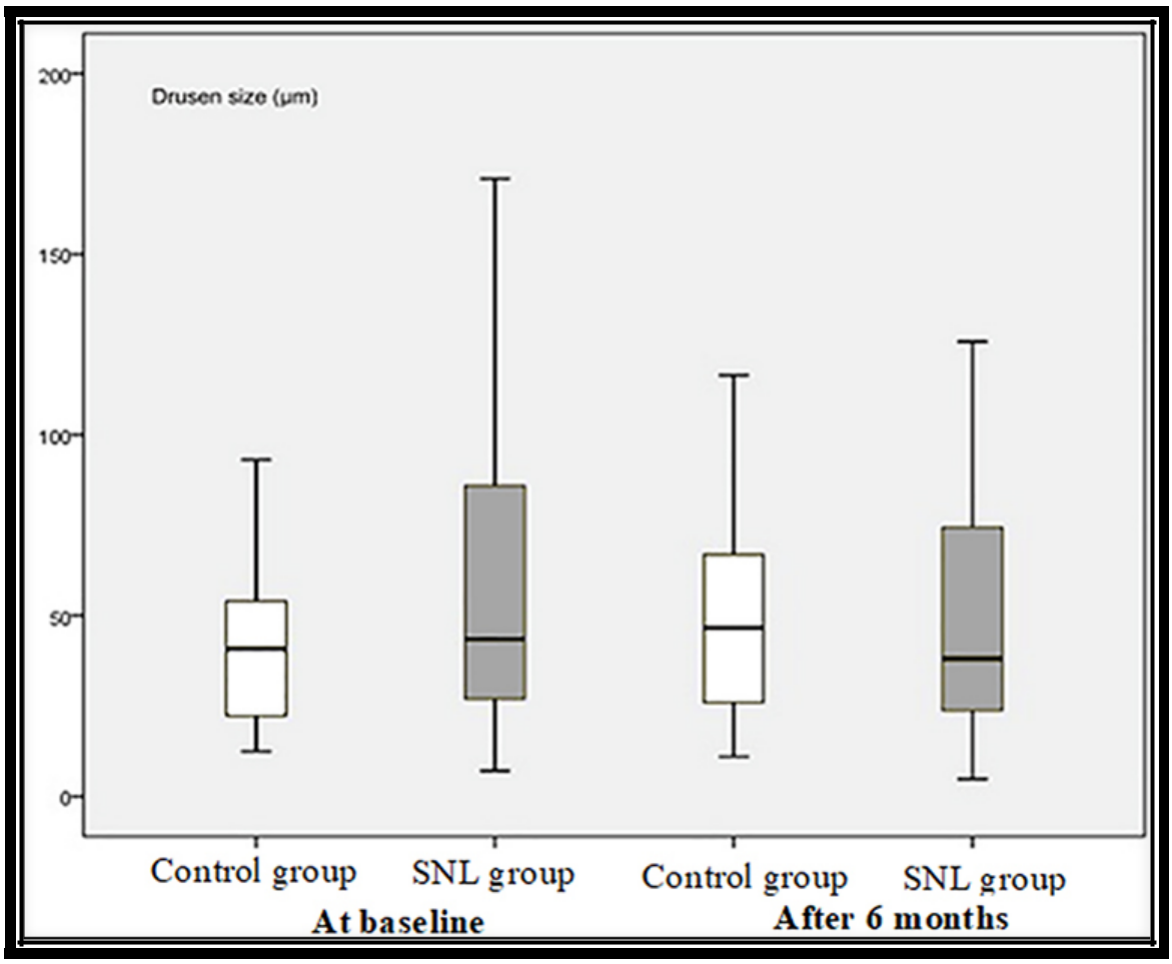

Figure 4 The drusen size (µm) in the control group at baseline was 40.6±20.3 (range=80.7, 12.4–93.1), after 6 months it was 49.3±28.4 (range=105.5, 11–116.5, *p*<0.001, 95% CI=39.4–59.2). In the SNL group, the drusen size (µm) at baseline was 59.9±44.8 (range=163.9, 7.1–171), and after 6 months it was 48.9±34.4 (range=121, 4.8–125.8, *p* <0.001, 95% CI=36.9–61) (26).

7.0 Tables

Characteristics	
Median Age (Years)	65
Gender	**N (%)**
Male	96 (45%)
Female	116 (55%)
Environmental and Systemic Factors	
Anti-Hypertensive Medications	79 (37%)
Cardiovascular Event History	65 (31%)
Smoking History	
Smokers	68 (32%)
Non Smokers	144 (68%)

Table 1: Representation of Baseline Characteristics for Patients Enrolled (SNL and Control Group) (26).

Secondary Outcome Measures	
Geographic Atrophy (GA)	
Total GA patients	198
Female GA patients	111 (56%)
Male GA patients	87 (44%)
Drusen Association with GA	167 (84%)
RPE Association with GA	31 (16%)
Hypo-pigmentation	6 (3%)
Choroidal New Vessels (CNV)	
Total CNV Patients	202 (95%)
Median age	65
Occult CNV	149 (73%)
Well-Defined CNV	40 (20%)
Vascularized Detachment	13 (6%)

Table 2 Measurement of Secondary Outcome Variables Geographic Atrophy and Choroidal New Vessels (26).