

AN OBSERVATIONAL STUDY ON THE EFFICACY AND SAFETY OF THE COMBINATION OF LUTEIN, VITAMIN C, ZEAXANTHIN, ZINC, COPPER, AND VITAMIN E IN INDIAN PATIENTS OF AGE-RELATED MACULAR DEGENERATION (AMD).

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Abstract.

Background:

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population, particularly those over the age of 65. The progressive decline in visual function experienced by individuals with AMD significantly impacts their daily lives and incurs their social activities and independence. This study aims to conduct a post-marketing investigation of a fixed-dose combination created for patients in India affected with AMD, evaluating its safety and efficiency.

Material and Methods:

In this research, a total of 450 participants were registered in the span of 10 months. The study was conducted at Anugrah Narayan Magadh Medical College, Gaya, Bihar. During the research, efficacy and safety assessments were conducted on every visit conducted after 3 months. The efficacy assessment involved the use of two parameters, namely vision-related quality of life (VRQOL) and vision impairment score, which were obtained by the administration of the Vision Impairment Questionnaire.

Results:

Assessing the patients with the help of vision impairment and VRQOL test, the following were the observations-

For the VRQOL test, on the 2nd and the 3rd visit, the VRQOL increased by 19% and 33% compared to the first assessment, this indicates a positive impact of the dosage administered. For the Vision impairment test, on visit 1 the percentage was 23% which further reduced to 15% by the second visit and 11% approx. for the third visit.

Conclusion:

After the successful investigation, the combination of Vit C (250 mg), Cu (1 mg), Zn (40 mg), Lutein (5 mg), Vit E (200 IU), and Zeaxanthin (1 mg) per capsule was determined to be both effective and safe in treating age-related macular degeneration (AMD) in Indian patients.

Recommendation:

It is recommended to consult an eye-care professional as soon as possible if vision changes and also continue to attend routine sight tests with an optometrist.

Keywords: Macular degeneration, Lutein, Vitamin C, Zeaxanthin, Zinc, Copper, Vitamin E,

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1. INTRODUCTION.

“Age-related macular degeneration” (AMD) is a complex ocular disorder that significantly diminishes the patient’s quality of life. Previous research has shown that the advancement and chances of AMD increase with age, with over 10% of individuals over the age of 80 experiencing late-stage AMD [1]. AMD majorly alters the macula, leading the new blood vessels to be fragile and can leak blood and fluid, leading to rapid and severe retinal vision loss. Early stage “Age-related macular degeneration” is some significant symptoms such as changes in the pigment of the retinal epithelium.

Advanced stage AMD manifests in two forms: neovascular which is wet or exudative and non-neovascular which is dry or non-exudative. Late-stage AMD leads to the deterioration of retinal vision, resulting in profound and enduring visual impairment and legal blindness. Therefore, this condition significantly diminishes the affected individuals’ quality of life and impedes their ability to perform daily tasks independently [2]. According to WHO’s report, “Age-related macular degeneration” is the foremost cause of blindness [3]. AMD is the most dominant cause of blindness globally, with AMD alone accounting for 8.7% of worldwide cases. In developing countries, such as India, the impact of AMD is particularly severe. Several notable studies have reported the occurrence of AMD in India which ranged between 1.5% to 1.8% [3].

Dry or non-exudative “age-related macular degeneration” is a recurring condition that typically results in visual disability in its early stages and can lead to potential total blindness. In contrast, the exudative “age-related macular degeneration”, also known as the wet form, affects only a small percentage (10-15%) of individuals with AMD. Exudative AMD manifests rapidly and, if not promptly treated, can rapidly progress to blindness [3]. Early AMD is characterized by common visual impairments, including mild distortion in the central vision and reduced ability

to read due to decreased luminance. Additional signs that may manifest include difficulty in recognizing faces and the presence of a central scotoma. However, individuals in this phase of AMD are typically asymptomatic. Advanced “Age-related macular degeneration” can lead to a sudden and rapid decline in visual function if it progresses to the neovascular form, while the atrophic form is characterized by a slow and gradual deterioration of central vision.

With the help of nutraceutical supplements incurable AMD can be prevented if not cured [4]. The macula lutea is situated centrally in the retina and harbors the most abundant population of photo-sensitive cells. Its primary function is to enable high-resolution visual activity. It contains “Lutein” and “Zeaxanthin” as a major components, and the macula lutea acts as a protective mechanism against photodamage. These compounds are capable of absorbing blue light and preventing severe harm to photoreceptors, “retinal pigment epithelium”. This absorption can reduce the amount of blue light reaching these structures by up to 90%, reducing oxidative strain on the retinal layer and lowering chances of advancement of “age-related macular degeneration” (AMD) [5, 6]. Clinical trials have demonstrated that Lutein is the most available in our body due to its fat-adhering nature. The approved daily dose of Lutein for AMD treatment is 20 mg [7]. Zinc is a component of antioxidant enzymes and is crucial for protecting the macula from oxidative damage.

In the case of “age-related macular degeneration”, particularly the dry form, zinc is part of a specific antioxidant and mineral combination recommended by the “Age-Related Eye Disease Study” (AREDS). This formulation, when used in the right dosage, can help reduce the chances of chronic AMD in individuals with intermediate AMD. While zinc is beneficial, its use should be discussed with a healthcare professional, as the specific formulation is essential, and high doses of zinc can have side effects [8]. Copper has been found to have a protective effect on the disintegration of “glutathione peroxidase” and “Superoxide dismutase” enzymes. Vit C is an antioxidant

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found in our blood, playing a crucial role in protecting "ocular tissues" from photo-oxidative damage by acting as a "free radical scavenger", thus contributing to the retinal defense mechanism [9]. Vitamin E, another antioxidant, helps to prevent reactions among the chemically free radicals in the eye. Vit E stabilizes the radicals by binding them to lipids, which is then restored to stabilize Vit E through interactions with substances like "Glutathione" or "Ascorbate" [10].

The investigation aimed to investigate the post-marketing surveillance of a fixed-dose combination for the treatment of AMD in Indians and to check its efficacy and safety. This combination consists of Vit C (250 mg), Vit E (200 IU), Zeaxanthin (1 mg), Zn (40 mg), Lutein (5 mg), and Cu (1 mg) per capsule, with a focus on treating AMD.

2. MATERIALS AND METHODS.

2.1. Study design and location.

The investigation was conducted at Anugrah Narayan Magadh Medical College, Gaya, Bihar.

2.2. Participants and study duration.

The study recruited a total of 450 patients, an average of 45 patients per day were investigated, the study started in September 2020 and ended in June 2021.

2.3. Inclusion criteria.

Patients of both genders were enrolled, with confirmed cases of AMD. Patients who signed the consent form and agreed to adhere to the rules and regulations of the study were considered.

2.4. Exclusion criteria.

All the patients who were registered for the study were asked to avoid supplements of Zinc, Zeaxanthin, Vit C, Cu, and Vit E. Patients with chronic issues, with intravenous injection treatment, and patients with other ocular diseases were exempted from the research.

2.5. Methodology and data collection:

The investigational dosage used in the study was a fixed combination including Vit C (250 mg), Cu (1 mg), Zn (40 mg), Lutein (5 mg), Vit E (200 IU) and Zeaxanthin (1 mg) per dosage, with a primary focus on treating AMD. Participants were instructed to take one capsule of the investigational product twice a day, with lunch and dinner, for a total span of 10 months. A medical background check was conducted for every patient and clinical records were maintained.

The study was conducted for 10 months and the participants were asked to visit the doctor after every 3 months. Considering the day 1 visit when the investigation started as (visit 1), the next visit after 3 months was (visit 2) and at 6 months (visit 3) and so on. Participants were provided with complimentary samples of experimental drugs and instructed to consume one capsule twice daily, with one in the morning and one in the evening, alongside a meal. The efficacy of the treatment was evaluated at baseline during visit 1 (day 0), and subsequently assessed during visit 2 and visit 3, along with safety considerations. The specific procedures employed for evaluating efficiency and safety are concisely outlined in the "efficacy assessment" and "safety assessment" sections.

The efficiency of the drug doses was evaluated using two parameters: "vision-related quality of life" (VRQOL) and vision impairment score, which were obtained through the administration of the vision impairment questionnaire. The vision impairment score is obtained from the reports of the vision impairment questionnaire. The efficacy of the investigational product was evaluated using two parameters: "vision-related quality of life and vision impairment score" attained from a vision disability questionnaire. A rating scale for the VRQOL is Table 1:

The secondary efficiency assessment was by administering the patients the "Vision Impairment Questionnaire" during visits 1, 2, and 3. They were instructed to select the corresponding answers provided in the table below. The score is calculated by adding the score of all ten questions.

The detrimental effects reported by the pa-

Table 1: **Rating Scale of VRQOL.**

Rate range	VRQOL assessment
1-2	Very poor
3-4	Poor
5-6	Average
7-8	Good
9-10	Very good

tients were categorized as either serious or non-serious. Additionally, a causality assessment was conducted using the WHO-UMC scale to determine the potential relationship between the investigational drug and the adverse effects. Throughout the 10 months, patients were prohibited from using any concomitant therapy, including neurotraceutical supplements containing Vit C, Lutein, Zeaxanthin, Zn, Cu, or Vitamin E. The investigational drug had already received approval for production and distribution in India.

3. RESULTS.

During the investigation, 450 patients were enrolled. Patients enrolled had AMD confirmed and consented to the treatment given to them. The result of this investigation is the culmination of all the scores under two categories, Efficiency assessment and safety test report respectively.

The efficiency report is contrived by calculating results via two parameters, which included a vision impairment questionnaire and VRQOL. The mean VRQOL score was calculated to be 5.23 which escalated to 6.88 on the 2nd visit and further increased to 7.45 on the 3rd (Table 2). On the 2nd and 3rd visits, the increased percentage in VRQOL turned out to be 19% and 33% of that compared to the first report. The 1st visit score was 20.5 which decreased to 18.00 by the 2nd visit and further decreased to 13.5 by the third visit. On visits 2 and 3, the percentage was reduced to 17.9% and 14.5% consequently as compared to the 1st visit score.

4. DISCUSSION.

The present research was done to test the efficiency of drug dosage of “Age-related macular degeneration” and the defensibility of the aggregation of Cu (1 mg), Vit C (250 milligrams), Lutein (5 milligrams), Zn (40 milligrams), Zeaxanthin (1 milligram), Vit E (200 IU) per dose for AMD affected patients. During the present investigation, the VRQOL score was 19% and 33% of that compared to the first assessment. In the case of the Vision impairment test, after the second and third visits, the percentage reduced by 18% in the second visit and 14% in the third visit as compared to the first one. The results of both tests indicated an improvement in visual functions among patients with “age-related macular degeneration” who received the drug in investigation. Additionally, no extreme adverse events were reported during the investigational study. During our investigation, it was found that the aggregation of Vit C (250 mg), Cu (1 mg), Zn (40 mg), Lutein (5 mg), Vit E (200 IU), and Zeaxanthin (1 mg) per capsule was determined to be both effective and safe in treating age-related macular degeneration (AMD) in Indian patients. Unlike the ARED trial, this dosage had minimal adverse effects and reduced the AMD in the patients. In the section below other research studies have been mentioned which are based on the same literature.

“Age-related macular degeneration” is a condition symbolized by the progressive damage of the “retinal pigment epithelium” and light-sensitive receptors located in the retina [4]. This degeneration is accounted for because of a combination of genetic factors, climatic influences, and advancing age, although other factors may also contribute [5]. A clinical study known as

Table 2: **Vision Impairment Questionnaire Score.**

S.No	Question for assessment	Option 1 No Diffi- culty	Option 2 Little Diffi- culty	Option 3 Moder- ate Diffi- culty	Option 4 Ex- tremely Difficult	Option 5 Insuffi- cient vision
1.	How difficult is it for you to read newspaper print?	0	1	0	1	1
2.	How difficult is it for you to do work that requires you to see well up close, such as cooking, sewing, fixing things around the house?	0	0	1	0	1
3.	How difficult is it for you to pick things from a cluttered shelf?	0	0	1	0	1
4.	How difficult is it for you to read name boards and street signals?	0	1	0	0	1
5.	How difficult is it for you to walk on stairs in dark?	0	0	0	1	1
6.	How difficult is it for you to notice things by your side when you're walking?	0	0	1	0	0
7.	How difficult is it for you to focus and watch movies or sports events?	0	0	0	1	1
8.	How difficult is it for you to do things like grooming, styling your hair etc.?	0	0	1	1	1
9.	How difficult is it for you to watch TV/Computer/Laptops?	0	0	0	1	0
10.	How difficult is it for you to read messages or dial numbers on mobile?	0	0	0	1	1
	Total	0	2	4	6	8

the "AREDS Clinical Trial" [11] was undertaken by the federal government's National Institutes of Health. This double-blind, placebo-controlled trial involved 3,640 participants, all aged between 55 and 80 years, who were diagnosed with age-related macular degeneration (AMD). The research was carried out at 11 different centers. Among the 3,640 subjects, 888 were assigned to get a combination of Vit C (500 milligrams), Vit E (400 IU), "beta-carotene" (15 milligrams), Zn (80 milligrams) as "zinc oxide", and Cu (2 milligrams) as "cupric oxide". Another 904 patients were randomly given zinc (80 milligrams) as "zinc oxide" and copper (2 milligrams) as "cupric oxide"

[12]. The results of the study showed that the risk of AMD advancement was reduced by 25% and vision loss was reduced by 19% in the subjects who received the combination of Vit C, Vit E, Zn, beta-carotene, and copper compared to those who received the placebo. The research determined that the aggregation of nutritional drugs, known as the "AREDS formulation" according to the NEI, consisting of Vit C (500 mg), Vit E (400 IU), beta-carotene (15 mg), Zn (80 mg) in the form of oxides, and Cu (2 mg) as its oxides, has the potential to decrease the likelihood of developing advanced "age-related macular degeneration" [13, 14].

After the success of 1st ARED trial, 2nd ARED clinical trial was conducted [13], to enhance the effectiveness of the AREDS drug dose by evaluating a new dosage that included lutein and zeaxanthin, which are present in high concentrations at the fovea, along with DHA and EPA. The objective was to research a therapy that could reduce the chances of AMD advancement. Additionally, the study mentions the impact of excluding β -carotene and adjusting the zinc dosage to 25 mg [15]. The results proved that the new drug dosage did not further decrease the risk of AMD advancement compared to the previous AREDS study. It was also recommended that the initial dosage should have included lutein and zeaxanthin without β -carotene. Based on the AREDS-2 findings, the recommended formulation for dry AMD now includes zinc, Vit C (500 mg), Vit E (400 IU), Zeaxanthin (2 mg), Cu (2 mg), lutein (10 mg) [15].

5. CONCLUSION.

After the successful investigation, the aggregation of Vit C (250 milligrams), Cu (1 milligram), Zn (40 milligrams), Vit E (200 IU), Lutein (5 milligrams), and Zeaxanthin (1 milligram) per capsule was determined to be both effective and safe in treating (AMD) in Indian patients.

6. LIMITATIONS.

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

7. RECOMMENDATION.

It is recommended to consult an eye-care professional as soon as possible if vision changes and also continue to attend routine sight tests with an optometrist.

8. ACKNOWLEDGEMENT.

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9. LIST OF ABBREVIATIONS.

AMD- age-related macular degeneration
VRQOL- vision-related quality of life
WHO- World Health Organisation
AREDS- Age-Related Eye Disease Study
UMC- Uppsala Monitoring Centre
NEI- National Eye Institute
DHA- Docosahexaenoic acid
EPA- Eicosapentaenoic acid

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11. CONFLICT OF INTEREST.

The authors report no conflicts of interest in this work.

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