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Comparing the Outcomes of Anti-VEGF Treatment for Choroidal Neovascular Membrane

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Abstract

This quasi-experimental study was conducted in the Department of Ophthalmology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, and Bangladesh Eye Hospital, Dhaka, Bangladesh, from March 2020 to August 2021, to compare the efficacy of Bevacizumab and Ranibizumab on patients with choroidal neovascular membrane (CNVM) due to age-related macular degeneration (AMD). A total of 34 eyes of 34 participants with CNVM in AMD divided into Group A, received monthly intravitreal ranibizumab (0.5 mg in 0.05 ml) and Group B, bevacizumab (1.25 mg in 0.05 ml) for 3 consecutive months. Before treatment, mean BCVA was found 37.9412±16.68259 in group A and 35.2941±12.68249 in group B. After treatment, the mean best-corrected visual acuity (BCVA) was found 53.5294±14.97547 in group A and 48.8235±13.75334 in group B. The differences were not statistically significant (p>0.05) between two groups. The improvement in BCVA was highly significant (p<0.0001) in both groups before and after giving intravitreal bevacizumab and ranibizumab. Before treatment, mean central macular thickness (OCT) was found in 344.8824±82.51582 µm in group A and 360.1765±82.22016 µm in group B. After treatment, OCT was found 255.18±71.852 µm in group A and 241.76±42.405 µm in group B. The differences were not statistically significant (p>0.05) between two groups. However, the improvement by decreasing macular thickness was highly significant (p<0.0001) in both groups before and after giving intravitreal bevacizumab and ranibizumab. Treatment with intravitreal bevacizumab or ranibizumab was associated with a similar improvement in mean visual acuity and decreasing central macular thickness by 4 months.

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Introduction

Age-related macular degeneration (AMD) causes irreversible blindness over 50 years. It is a complex natural disease with genetic and environmental aetiology.[1] Nearly 11 million people suffer from dry AMD, and 1.5 million have wet AMD in the USA.[2] Despite the introduction of new therapies, the rate of AMD is expected to increase by 97% by 2050.[3] The advanced form of the disease impacts more than a million individuals,

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adversely affecting their quality of life and activities of daily living and causing many individuals to lose their independence in their retirement years. Various therapeutic options, including anti-vascular endothelial growth factor (VEGF) agents and photodynamic therapy (PDT), have been reported to manage CNV.[4]

Currently, anti-VEGF therapy is the main treatment option. Anti-VEGF in CNV treatment includes ranibizumab, bevacizumab, brolicizumab, aflibercept, and pegaptanib sodium.

Ranibizumab (Lucentis; Genentech/Novartis) is an anti-VEGF agent developed for intraocular use. It recognises all five VEGF human isoformsGF and is a monoclonal antibody fragment. It decreases vascular permeability and blocks angiogenesis by penetrating all layers of the retina.[5] In clinical trials, it is delivered as monthly intravitreal injections to stop and reverse some vision in neovascular AMD.[6,7] Anatomical improvement was observed following intravitreal ranibizumab injection by optical coherence tomography (OCT) associated with a reduction in intraretinal and subretinal fluid. On fundus, fluorescein angiography (FFA), inhibition of neovascular growth and leakage in a range of lesion types was observed. These positive findings make ranibizumab the most effective, FDA-approved treatment currently available for more neovascular forms of AMD.[8]

Bevacizumab (Avastin; Genentech Inc.) is also an anti-VEGF agent and a monoclonal antibody; it was licensed to treat colorectal cancer in 2004.[9] It is derived from the same murine anti-VEGF antibody as ranibizumab. It is used as an off-label treatment for age-related and myopic choroidal neovascular membranes. The promising results obtained with bevacizumab have raised the expectations of retina specialists and patients.[10,11] In the case of bevacizumab, it is a cheaper alternative than ranibizumab and gives multiple doses from a single vial, which is helpful for lower-income individuals with advanced AMD.[12,13]

The cost difference between these two drugs is highly significant for individuals with no or limited health insurance benefits because of the cheaper alternative, bevacizumab, used by many eye doctors around the world as an off-label intravitreal agent.[14] Bangladesh is the least developed country, so this cost difference assumes a greater significance in the Bangladeshi scenario. Thus, there is a very urgent need to conduct large multi-centric studies comparing these two drugs concerning their efficacies and safety profiles. Our study aims to compare the efficacy of intravitreal ranibizumab and bevacizumab in treating CNVM due to AMD in the Bangladeshi scenario. It will help our patients to continue the treatment as patients need frequent injections of these two drugs at monthly intervals.

Methods

The quasi-study was conducted at the Department of Ophthalmology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, and Bangladesh Eye Hospital, Dhanmondi, Dhaka, from March 2020 to August 2021.

The inclusion criteria for the study were: i) Patients older than 50 years and ii) Patients with baseline best corrected visual acuity (BCVA)

between 10 and 70 ETDRS letters. iii) Central macular thickness more than or equal to 220 µm. iv) All cases of CNVM v) Cases with active leakage pattern. vi) No previous treatment for CNVM in either eye.

The exclusion criteria for the study were i) Macular scarification. ii) Coexisting other ocular pathology. iii) One-eyed patients. iv) History of ocular surgery within the last six months. v) History of cerebrovascular accident and myocardial infarction vi) Use corticosteroids or any other drug that affects the macula, including chloroquine, hydroxychloroquine sulfate thioridazine, and chlorpromazine. vii) Any mental, social or physical condition affecting regular follow-up.

A total of 34 eyes of 34 participants with choroidal neovascular membrane in age-related macular degeneration were assigned to receive intravitreal ranibizumab (17-group A) and bevacizumab (17-group B). Patients were subjected to visual acuity testing, intraocular pressure measurement by applanation tonometry, Amsler Grid assessment, slit-lamp examination and biomicroscopy after pupillary dilatation using +90 diopter (D) lens and indirect ophthalmoscopy. Patients suspected to have wet AMD will be referred to the retina clinic for digital fundus fluorescein angiography and optical coherence tomography (OCT) to reach a definite diagnosis of CNVM formation.

Procedure of Intravitreal injection: The patients in group A will be given intravitreal injections of 0.5 mg ranibizumab (Lucentis) in 0.05 ml in the operation theatre, taking full aseptic measures for three consecutive months (Months 0, 1 and 2). Similarly, the patients in group B will be given intravitreal injections of 1.25 mg bevacizumab (Avastin) in 0.05 ml in the operation theatre, taking full aseptic measures on three consecutive months (Months 0, 1 and 2). Patients were scheduled to have follow-up examinations immediately the next day after giving the 1st injection, and the final follow-up was four months later. The first visit was done to assess the visual acuity or any complications or side effects. In 4th month, BCVA and OCT were done. Outcome measures included changes in BCVA, central macular thickness and occurrence of complications.

This research was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Results

A total of 34 eyes of 34 participants with CNVM in age-related macular degeneration were equally categorized into two groups, i.e., 17 in each group (Group A and Group B) assigned to receive intravitreal ranibizumab (group A) and bevacizumab (group B). The mean age was 66.82±13.68 years in group A and 68.06±9.13 years in group B. In group A, 11 patients were male and six were female; in group B, ten were male, and seven were female.

Before treatment of the study patients, the mean BCVA was found to be 37.94±16.68 letters in group A and 35.29±12.68 letters in group B. The difference was statistically insignificant ($p>0.05$). The mean IOP was 14.55±2.56 in group A and 12.55±1.88 in group B. Before giving an injection, mean macular thickness (OCT) was found to be 344.88±82.51 µm in group A and 360.17±82.22

µm in group B (p>0.05) (Table-I). After treatment, the mean BCVA was 53.5294±14.97547 in Group A and 48.8235±13.75334 in Group B, and the mean central Macular thickness was 255.18±71.852 in Group A and 241.76±42.405 in Group B. Before treatment, the mean BCVA was found 37.9412±16.68259 in group A and 35.2941±12.68249 in group B. After treatment, the mean BCVA was found to be 53.5294±14.97547 in group A and 48.8235±13.75334 in group B (p>0.05).

However, the improvement in BCVA was highly significant in both groups before and after giving intravitreal bevacizumab and ranibizumab (Table-II).

In Table-III, before treatment, mean BCVA was found to be 37.9412±16.68259 in group A and 35.2941±12.68249 in group B. After treatment, mean BCVA was found to be 53.5294±14.97547 in group A and 48.8235±13.75334 in group B (p>0.05). However, the BCVA improvement was highly significant in both groups before and after giving intravitreous bevacizumab and ranibizumab.

In Table-IV, before treatment, mean central macular thickness (OCT) was found at 344.88±82.51µm in group A and 360.17±82.22µm in group B. After treatment, mean central macular thickness (OCT) was found to be 255.18±71.852µm in group A and 241.76±42.40µm in group B (p>0.05). However, the improvement by decreasing macular thickness was highly significant in both groups before and after giving intravitreous bevacizumab and ranibizumab. Observed complications were: 3(17.6%) patients had pain in group A and 5(29.4%) in group B, while 4(23.5%) patients had a subconjunctival haemorrhage in group A and 5(29.4%) in group B. IOP increased in 4(23.5) patients in group A and 2(11.7%) in group B, but but this increase was within the normal range of IOP.

The rest of the patients in both groups had no complications. Those immediate injection-related complications were not significantly different between the two groups (p>0.05).

Table-I: Distribution of study patients by Ocular examination before injection (n=34)

Ocular Examination	Group A (n=17) Mean±SD	Group B (n=17) Mean±SD	p-value
BCVA	37.9412± 16.68259	35.2941± 12.68249	0.6061
Range (min, Max)	10.00, 70.00	20.00, 70.00	
IOP	14.55±2.56	12.55±1.88	
Range	11, 19	10, 18	
OCT (µm)	344.8824± 82.51582	360.1765± 82.22016	0.5919
Range (min, Max)	222.00, 468.00	236.00, 504.00	

BCVA in ETDRS letter visual acuity, p value was reached from unpaired t-test

Table-II: Distribution of study patients by BCVA and OCT after 4 months (1 month after 3rd injection)

After 4 months	Group A (n=17) Mean±SD	Group B (n=17) Mean±SD	p-value
BCVA	53.5294± 14.97547	48.8235± 13.75334	0.347
Range (min, Max)	35.00, 75.00	35.00, 75.00	
OCT (µm)	255.18±71.852	241.76±42.405	0.5120
Range (min, Max)	(135,424)	(196.361)	

BCVA in ETDRS letter visual acuity, p value was reached from unpaired t-test

Table-III: BCVA before and after treatment (after 1 month of giving 3rd injection)

BCVA	Group A (n=17) Mean±SD	Group B (n=17) Mean±SD	p-value
Before	37.9412± 16.68259	35.2941± 12.68249	0.6061
After	53.5294± 14.97547	48.8235± 13.75334	0.3471
P value (before and after)	b 0.0001s	b 0.0001s	

BCVA in ETDRS letter visual acuity

Table-IV: OCT before and after treatment (after 1 month of giving 3rd injection)

OCT	Group A (n=17) Mean±SD	Group B (n=17) Mean±SD	p-value
Before	344.8824± 82.51582	360.1765± 82.22016	0.5919
After	255.18± 71.852	241.76± 42.405	0.5120
P value (before and after)	0.0001	0.0001	

Discussion

Our quasi-experimental study investigated the effect of intravitreal Bevacizumab or ranibizumab treatment on the choroidal neovascular membrane in age-related macular degeneration, causing decreased visual acuity. After four months of treatment, the study demonstrated a significant improvement in visual acuity and decreased central macular thickness. Two agents produced similar results. The study population in both groups had similar demographic, clinical and biochemical characteristics before treatment, although randomization could not be done. The ANCHOR[15] and MARINA[16] Trials have provided detailed information on the effectiveness of intravitreal ranibizumab in treating neovascular AMD. ANCHOR study showed results at 12 months and 24 months. The VA improvement from ranibizumab was statistically significant and clinically meaningful. 89.9% of patients in the 0.5mg ranibizumab group and 90.0% of patients in the 0.3mg ranibizumab treated group had lost less than 15 letters from baseline.34% in the 0.3-mg ranibizumab group, and 41.0% in 0.5-mg ranibizumab group had gained 15 or more letters; and, on average, VA was improved from baseline by 8.1 to 10.7 letters. The MARINA study found that 94.5% of patients receiving 0.3 mg and 94.6% receiving 0.5 mg experienced a decrease in visual acuity of more than 15 letters from baseline. After 12 and 24 months, around 25% of those who received 0.3 mg of ranibizumab and approximately 33% of those who received 0.5 mg of ranibizumab achieved a gain of 15 or more letters in visual acuity.

The efficacy of Bevacizumab has been demonstrated a significant improvement in visual acuity within one week of treatment.[17,18] By 12 weeks, the median and mean VA letter scores showed increases of eight and 12 letters, respectively. The median and mean central retinal thickness measurements decreased by 157 m and 177 m, respectively.[16] The study conducted by Avery revealed that mean and median vision improved at 4 and 8 weeks, with the former improving from 20/200 to 20/125 and the latter improving from 20/200 to 20/80 at both 4 and 8 weeks. Retinal thickness reduced at 1, 4, 8, and 12 weeks by 61, 92, 89, and 67 m, respectively.[18] Bashshur *et al.*[19] show that the mean baseline BCVA was 20/252, and the baseline CRT was 362 m. After 12 weeks, the mean BCVA was 20/76 and the mean CRT

decreased to 211 m. No side effects, either systemic or ocular, were observed at any point in time. They concluded that eyes with CNV due to AMD treated with intravitreal Bevacizumab had marked anatomic and visual improvement. Further studies are necessary to confirm this treatment's long-term efficacy and safety.

No significant difference was found in BCVA or CMT change between the ranibizumab and bevacizumab groups after the 3rd intravitreal injection at four months of follow-up. Both were equally productive in improving BCVA (functional improvement) or CMT (structural improvement).

CATT trial[20] concluded as Vision gains during the first two years of the trial were not maintained at five years. However, 50% of eyes had VA 20/40 or better, confirming anti-VEGF therapy as a major long-term therapeutic advance for neovascular AMD. IVAN trial[21] found there is similar efficacy between Ranibizumab and Bevacizumab. The LUCAS study found that Bevacizumab and ranibizumab had an equivalent effect on visual acuity after one year when administered according to a treat-and-extend protocol.[22] According to the GEFAL study, Bevacizumab and ranibizumab had similar safety profiles and were non-inferior in terms of visual acuity after one year. Ranibizumab appeared to have a better anatomical outcome. These findings are similar to previous head-to-head studies.[23] The MANTA study found that Bevacizumab and ranibizumab had equivalent visual acuity results throughout one year. There was no significant difference in the decrease of retinal thickness or number of adverse events.[24]

Bevacizumab and ranibizumab have similar effects on visual acuity and macular thickness. These gains were documented each month following the injection. Intravitreal Bevacizumab is as safe and effective as intravitreal ranibizumab in treating exudative AMD. Several studies reported on the management of the patients with neovascular AMD who switched from Bevacizumab to ranibizumab therapy.[16,17,25] They concluded no significant differences in visual acuity outcomes or injection rates. Fong *et al.* found no difference in Visual outcome between Bevacizumab and Ranibizumab treatments, both of which were effective in stabilizing VA loss.[26] Biswas *et al*. found Ranibizumab and Bevacizumab equally effective and safe for treating CNVM caused by AMD.[27] Subramanian *et al*.[28] showed that early results of a head-to-head, randomized, double-masked, prospective, single-centre controlled trial between Bevacizumab and ranibizumab show no difference in efficacy between the two treatments. The BRAMD Study shows Bevacizumab was not inferior to ranibizumab.[29]

According to Chang *et al*.[30], the effectiveness of ranibizumab treatment in the short term, as measured by the incremental improvement in optical coherence tomography parameters, was significantly higher than that of bevacizumab treatment. This suggests that there may be distinct differences in the biological activities of ranibizumab and Bevacizumab.

It is worth noting that neither group experienced any significant adverse effects. This is a promising sign that the intervention could be a safe and effective alternative. Subconjunctival bleeding, increased intraocular pressure (IOP), and mild ocular pain were the most common. There were no complications reported among the other patients in both groups. These immediate

injection-related complications were not significantly different between the two groups. These observations align with Mojica *et al*.[31], Fung *et al*.[32], and the PIER study.[33] No endophthalmitis, lens injury or retinal detachment was observed in any of the patients in our study.

Our quasi-experimental study was conducted across two centres in Dhaka, Bangladesh. The study investigated changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) and the adverse effects of both drugs. No significant difference found in efficacy and safety between ranibizumab and Bevacizumab for CNVM treatment due to wet AMD.

Thus, from our present study, we can conclude that both ranibizumab and Bevacizumab are safe and efficacious treatment options as intravitreal injections in the treatment of CNVM due to AMD and that the two do not have statistically significant differences between them in terms of bringing about BCVA and CMT improvement. In this Study, Participants and outcome assessors were aware of the treatment group assignments.

Conclusion

Both ranibizumab and bevacizumab are safe and effective treatment options as intravitreal injections for the treatment of CNVM due to AMD, and the two do not have statistically significant disparity between them in improving BCVA and CMT. However, more studies with larger sample sizes are essential to establish statistical significance, as this study only contains results from a small number of patients.

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