Volume. 1 Issue No. 2 (2025)

Pakistan Journal of Medicinal Science

OPTIMIZING TREATMENT PROTOCOLS FOR DIABETIC MACULAR EDEMA: A COMPARATIVE STUDY OF SINGLE VS. MULTIPLE INTRAVITREAL ANTI-VEGF INJECTIONS

Imran Ullah
School of Health Sciences, Peshawar.
Noor Ullah
Lecturer, School of Health Sciences, Peshawar.

ABSTRACT:

Objective:

The aim of the research study is to evaluate single versus multiple intravitreal anti-VEGF injections in patients with diabetic macular edema (DME) with respect to the effect of different number of injections on the visual acuity, macular thickness and patient's outcome at 12 months of follow up.

Study Design: It is a longitudinal experiment and it was carried out in tertiary care ophthalmology center.

Methods: Sixty patients with DME were randomly allocated into two groups whereby one study group would receive a single intravitreal injection of anti-VEGF therapy and whereas, in the other group of patient's multiple intravitreal injections (namely three) of anti-VEGF would be administered over the period over which the study lasted. Primary outcome measure was the change in the best-corrected visual acuity (BCVA), and second results was macular thickness using optical coherence tomography (OCT).

Results:

The patients who were administered with the multiple injections exhibited a higher improvement in BCVA (average of 8 letters) as compared to those who were administered with a single injection (average of 4 letter) ($p<0.05$). There was also an enhanced reduction in macular thickness in the multiple injection group (a mean decrease of 150 microns) with a lesser decrease in the single injection group (a mean decrease of 80 microns).

Conclusion:

More injections of anti-VEGF intravitreal agent provide better outcomes in managing DME compared with one intravitreal injection and result in better visual acuity and macular thickness. This finding implies that anti-VEGF drugs applied more often might show improved clinical result of DME patients.

Keywords:

Diabetic macular edema, anti-VEGF, intravitreal injections, treatment protocol, visual acuity, macular thickness, longitudinal study

INTRODUCTION:

The delayed complication of diabetic retinopathy (DR) (diabetic macular edema/DME) is one of the most prevalent and incapacitating diseases of adults (below 65 years of age) throughout the world. DME is a kind of eye disorder which occurs due to an increase in the sugar level of blood attributed to diabetes that causes the blood vessels located in the retina to suffer damage since the fluid is forced to escape to the macula or the central faculty of the retina that enables an individual to see clearly. Since this fluid

buildup makes the macula swell, it affects the Central visualization and, ultimately, results in a large number of effects (both functional and quality of life). (Cheung et al., 2010). The occurrence rate of DME has progressively grown over the past several years, which is the result of the rise in the rate of diabetes cases globally. It has been observed that out of every 5-10 diabetics, about 20-30 percent develop some level of DME in their lifetime (Yau et al., 2012), which necessitates the administration to the research of sustainable and effective treatment plans to manage this case.

The overproduction of vascular endothelial growth factor (VEGF) is the major pathogenesis process of DME which is a protein that helps the synthesis of new blood vessels. When it comes to diabetes, chronic hyperglycemia will cause the retinal vasculature to malfunction resulting in disintegration of the blood-retina barrier, resulting in the ability of plasma proteins and lipids to build up at the macula. A key protein in this process is VEGF which causes the vascular permeability to increase and get abnormal angiogenesis in the cardiovascular system that leads to development and progression of DME (Wang & Lo, 2008). The loss of retinal endothelial cells and build-up of extravascular fluid in the macula lead to thickening of the retina subsequently, which leads to the occurrence of DME, i.e. the loss of central vision.

Early intervention in the management of DME cannot be over emphasized. DME has the potential to cause vision impairment and severe disability in the absence of proper treatment. In addition, the cost of treating diabetic eye diseases is high economically where the direct cost consists of treatment through medical claims and the indirect cost consisting of the productivity loss in the labor market (Zhao et al., 2017).

Anti-VEGF therapy has transformed the treatment of DME in the last twenty years. They are monoclonal antibodies, which include ranibizumab (Lucentis), aflibercept (Eylea) and bevacizumab (Avastin) as anti-VEGF agents that prevent the activity of VEGF. These medications decrease permeability of retinal vasculature and production of aberrant blood vessels by binding with VEGF and blocking its connection to cell receptors of endothelial cells, leading to the effective decrease of macular edema and vision improvements (Campochiaro et al., 2015). Anti-VEGF therapy has proved to be effective in treating DME with several clinical studies and is currently used as the first line of therapy in the condition (Elman et al., 2010).

RISE and RIDE trials, to give an example, revealed that the intravitreal injections of ranibizumab have drastically enhanced visual acuity and decreased the central retinal thickness in DME patients (Campochiaro et al., 2015). Likewise, the efficacy of aflibercept in DME was proven in the VISTA and VIVID trials that demonstrated the same effect on visual acuity and macular thickness (Heier et al., 2016). The trials were strong points in showing that anti-VEGF agents have the potential of making massive improvements in the anatomical as well as functional outcomes of DME. Thereafter, the treatment of DME has been reshaped into the use of anti-VEGF injections.

Although anti-VEGF agents have proven to be effective, one of the current disappointments regarding the care of DME is the amount of dosing. Conventionally, gene injections are done frequently like in a monthly basis during the initial months, and

afterward stabilization injections are done at a lesser frequency. Nevertheless, this method may cause significant treatment burden to patients when they have to go to office regularly, get injections and bear the corresponding expenses (Elman et al., 2010). More injections also lead to probable complications including, ocular infections, retinal detachments, and endophthalmitis making it more difficult to treat the patient.

Due to this, interest has been growing in understanding whether less frequent dosing strategies, either less frequent administration at first and then as-needed (PRN)-based treatment or a fixed-dose maintenance treatment, would provide a comparable or improved outcome with respect to both efficacy and safety. This idea of customized or flexible treatment plans is to prevent the overburdening of the patients with regards to treatment cost and time and to ensure the effectiveness of the anti-VEGF treatment. Nevertheless, it is controversial how to define the most appropriate frequency of injections.

The Protocol T study that compared the results of monthly injections with PRN approach in using ranibizumab aided in the realization that both strategies were effective in improving visual outcomes, but patients receiving more frequent injections had better results regarding visual acuity (Elman et al., 2015). These existing results reveal the complexity of the dosing strategy to treat DME and the necessity to conduct additional research to investigate the long-term results of various injection regimens.

Considering that the best treatment course is unclear, this undertaking aims to compare the effects of single intravitreal injection of anti-VEGF to multiple injections among the cases of DME. Though there might be short term benefits of using single injection regimens it is yet unknown whether a single injection would give long term improvement in the visual acuity and macular thickness as well. Alternatively, though, the more efficient method might be multiple injections, which, however, would have several drawbacks, such as an increased price, burden, and risk of some adverse events (Wells et al., 2016).

The literature containing the conflicting evidence exists on the number of injections needed to get the optimal DME management. A study named RESTORE trial designed to assess the performance of a flexible dosing protocol ranibizumab revealed that monthly ranibizumab injection resulted in a substantial increase in the visual acuity along with the reduction in the macular thickness (Mitchell et al., 2011). Nevertheless, such treatment was too demanding on patients, and researchers tried to explore less intensive treatment regimes. However, on the contrary, the VIVID and VISTA trials provided an answer that three initial monthly shots of the drug and subsequent flexible regimen of as-needed injections led to equitable enhancements in visual acuity between continuous monthly shots of the drug and a flexible protocol of as-needed injections (Heier et al., 2016). The results connote that a plan of reduced injections is potentially equally successful in the long-run.

A relative comparison of the efficacy of a single injection intervention and a multiple injections intervention is an unresolved topic, and it is important that we realize how each method affects treatment outcomes, macular edema resolution and the comfort of

the patients. Moreover, to come up with the most feasible treatment regimen of DME patient especially in poor settings, it is important to understand the cost-effective nature of these two approaches.

The findings of such study are likely to yield invaluable information in refining the protocols of treating DME. In case several injections are shown to yield better results, this situation can bring up the changes in clinical practice to more frequently dosing in patients with more natural development of DME. Alternately, in the case that single-injection regimens are found equally effective it would both ease the treatment burden on the patients and will also ease the healthcare expenses on the DME treatment process. Finally, the study will provide vital information used to make clinical decisions and create more personalized and effective methods of treating DME.

In addition, the results of the current study can potentially be extended to include the treatment of other retinal diseases with less specific focus on age-related macular degeneration (AMD) and retinal vein occlusion (RVO), which, in turn, are also often used as services of anti-VEGF agents. Seeing that the pathophysiology of these conditions is similar, the findings of this study may affect the bigger picture of anti-VEGF therapy in retinal practice.

MATERIALS AND METHODS

Study Design:

In this study, a longitudinal, experimental research design was used to determine the effectiveness of one intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection and repeated intravitreal injections in patients with diabetic macular edema (DME). Longitudinal studies are also quite useful in assessing the effect of clinically applied procedures with long-term implications since they facilitate the measurement of patient outcomes over a long duration and this is crucial in understanding whether the treatment effect is sustainable. Participants were evaluated over 12 months in this study, which allowed getting to know some time-specific peculiarities of visual acuity, macular thickness, and patient outcomes altogether.

The research was done in a tertiary care ophthalmic institution, which offered access to highly-advanced diagnostic equipment and skills required in handling more complicated cases regarding diabetic retinopathy and macular edema. Specialist equipment as well as medical personnel who are able to offer a high quality service to patients with severe or progressive ocular disease abnormalities are located at tertiary care centers. The clinical environment permitted high-resolution imaging technology such as optical coherence scanning technology (OCT) imaging of macular thickness, and also, experienced ophthalmologists could administer injections and check on the patient progress in the period of study.

Since DME is a chronic progressive condition, one year of follow up was imperative in order to assess the immediate and long term impacts of treatment. The 12-month follow up enables examining whether there are any changes in the retina structure and functionality over the period during which the patients are treated as well as identifying the complications or side effects that might emerge in the process of treatment. The

main concepts of the study were to correlate the visual results and the variations in macular thickness between single and several-injections groups and compare it to ascertain the most superior treatment plan in the management of DME.

Participants:

In the study, sixty patients with DME were used. The study required study participants to be recruited through the ophthalmology clinic at the study center, and several relevant inclusion and exclusion criteria were enforced to recruit relevant individuals who fit the required diagnostic and demographic criteria. The inclusion and exclusion criteria were to maximize minimal confounding factors and allow generalizability of the study population to the rest of the population with DME.

Inclusion Criteria:

Depending on the type of Diabetes Type 1 or Type 2 Diabetes: To allow the outcome of the study to be applied to a large type 1 or type 2 diabetic population only patients with an already established diagnosis of either type 1 or 2 diabetes mellitus were to be included or considered. The leading risk factor of developing DME is diabetes and the incorporation of both types of diabetes will enable the study to determine the outcome of treatment on a wide spectrum of diabetic patients. Past researches revealed that DME is highly associated with diabetes type 1 and type 2 (Cheung et al., 2010; Yau et al., 2012).

Clinically Significant Diabetic Macular Edema (DME): Only patients with clinically significant DME were involved, which is determined by the aspects of retinal thickening within the central macula, as well as leakage in retinal vessels on OCTs. The most dangerous form of DME is the clinically significant one since it poses the highest risk of impaired vision and is thus the most important one to treat (Wells et al., 2016). Diagnostic OCT could measure the exact thickness of retina and be positive in proving the degree of edema severity, which is essential in deciding the suitable treatment methods.

Best-Corrected Visual Acuity (BCVA) Between 20/40 and 20/400: The baseline of the visual acuity of the participants was to be 20/40 to 20/400 of the Snellen chart. This range portrays moderate to severe impairment of sight which is common among patients with DME. The reason behind enrolling patients whose visual acuity falls in this range is that by doing so, it is possible to assess meaningful changes to a patient regarding their visual functioning, since very low visual acuity patients (e.g. <20/400) are unlikely to demonstrate they have improved their vision with treatment, making the results difficult to interpret.

Willingness to completing Study Protocols: Since the study spanned over a long period and would require frequent follow-ups, the study subjects required willingness to comply with the study protocol. This also covers being present to take long overdue visits, undergoing intravitreal injections based on treatment schedule and adherence to the evaluation methods including OCT scan and BCVA examination.

Exclusion Criteria:

Active Retinal or Eye Infection: Infected patients with any active eye or retinal infection e.g. endophthalmitis and uveitis patients were excluded. There might be infections that interrupt the healing process following injections and these infections may contaminate the study results (Jampol et al., 2017). The participants were needed to have healthy eyes to make sure that the alterations in visual acuity and macular thickness could not be explained by other factors except the anti-VEGF therapy.

History of Intraocular Surgery (Not Cataract Surgery): Patients with known history of intraocular surgery e.g. repair of the detachment of the retina, glaucoma surgery, laser etc were excluded. Such processes might change the way the retina reacts to anti-VEGF treatment, which may subsequently present confounding variables that will disrupt the study outcomes (Tufail et al., 2018). They only considered the individuals who had not yet had any retinal surgery aimed at avoiding the chances of classifying the changes as a result of other interventions.

Non-Diabetic Retinal Conditions: Patients that do not have some retinal conditions connected to diabetes e, g, age-related macular degeneration (AMD), retinal vein occlusion (RVO), etc. were discussed as excluded. The conditions can elicit the same symptoms as DME yet the responses to their treatment and pathophysiology are different. This dropped the patients with non-diabetic retinal problems who would have compromised on the study aim of determining the impact of the anti-VEGF therapy in DME (Mitchell et al., 2011).

The data were measured at the baseline, after 6 and 12 months to monitor the change of clinical parameters and treatment outcomes over the course of time. This set consisted of a complex of medico-clinical examinations, examinations with the use of imaging, and examination of past illnesses. The gathered data was important to determine the efficiency of the treatment regimens in context of visual acuity, thickness of the maculas and demographics of the patients.

Best- Corrected Visual Acuity (BCVA):The measurement of BCVA relied on standard practice with the Snellen chart on the baseline, 6 months, and 12-month levels. Snellen chart is a common device in the ophthalmic practice of measuring visual acuity. The best single line which a patient reads correctly is his visual acuity. The effectiveness of the anti-VEGF injections was done using BCVA measurements which were the primary outcome measure. An improvement in the BCVA within the study eliminates the possibility of an eventual decline in the visual impairment level, which would mean the visual functioning will be improved by the treatment (Wells et al., 2016).

Optical Coherence Tomography (OCT): Optical Coherence Tomography was also carried out at baseline, 6 months and 12 months as assessment of variation of macular thickness. OCT is a high resolution, cross-sectional image driven technology that is non-invasive. OCT can determine thickness of the central macula and evaluate the level of edema, as well as its decrease over an established period of time. The decrease in the thickness of the macular would imply the successful specific treatment based on the application of anti-VEGF therapy (Campochiaro et al., 2015).

Demographics and Medical History:A demographic questionnaire was obtained on each participant who was enrolled. Data about age, gender, years of diabetes diagnosis, and comorbidity with such diseases as hypertension or diabetic nephropathy were noted. These are factors that have been known to shape the development of DME, and might as well play a role in the treatment outcome (Cheung et al., 2010). Depending with the inclusion of such variables to the analysis, potential confounding factors were managed in the analysis.

The Statistical Package for the Social Sciences (SPSS) was used to get statistic results. Analysis was done based on within-group and between-group comparisons to evaluate the impacts of the two regimes on the visual acuity and the thickness of the macula.

Within-Group Comparisons: Paired t -tests were used to compare the changes of BCVA and the thickness of the macula in individual different groups between base line and 6 months and base line and 12 months. Analysis of such kind of data is suitable to be evaluated using paired t-test because of the correlation between two measurements taken at different time points among the same participants to determine the effect of treatment at different times (Tufail et al., 2018).

Between-Group Comparisons: In a bid to compare the effect that was observed in the single- injections and multiple injections groups, an independent t-test was used. In this test, the means of the two independent groups are compared in order to ascertain whether there is a significant variation between their treatment outcomes. It was decided that a p-value of less than 0.05 was significant (Wells et al., 2016).

The ethical approval issued by the ophthalmology center institutional review board (IRB) made the study ethical in terms of the requirements of ethics in undertaking human research study. It is also important to note that all of the participants were informed and fully briefed about what the study was, the procedures that will take place, potential risks and its advantages. The study has complied with ethical policy in Declaration of Helsinki, which sustains focus on upholding the rights of participants and upholding the integrity of research process. The study was conducted in confidence and all the information stored safely and only used to conduct the study (World Medical Association, 2013).

RESULTS

The sample was comprised of 60 participants, all people with diabetic macular edema (DME). The median age of respondents was 62 years old with the ratio of 2:1 between males and females meaning that there is a majority of male patients. The age range corresponds to the one that can be affected by DME since the condition is usually exhibited in patients with a history of chronic diabetes (Yau et al., 2012). Most of the participants included T2DM which made up 85 percent of the sample with 15 percent having T1DM. This increases the prevalence of T2DM according to the current trend where type 2 diabetes is more prevalent and also accounts to the increased burden of diabetic complications such as diabetic retinopathy and DME (Cheung et al., 2010).

The two groups, including those injected once and the groups injected multiple times had similar baseline characteristics. The demographic information did not indicate any

material variations in the age, gender ratio, and the ratio of type 1 and type 2 diabetes between the two parties. This was necessary to make sure that the effects observed could be categorized as a result of the treatment regime and not as a result of demographics factors or disparities of the groups regarding their baseline profile.

In addition, the length of diabetes had a range in the study population with a mean of 12 years with diabetes. The established fact is that the duration of diabetes frequently has the influential role in developing and progression of DME because retinal microvascular alteration may be caused by prolonged hyperglycemia, posing the higher risk of edema and other complications (Wells et al., 2016).

The mean visual acuity with best correction (BCVA) in the single-injection group at baseline was 55 letters and multiple-injection group had a mean baseline visual acuity of 56 letters. BCVA was measured using the Snellen chart with each letter accounting to a 5-letter greater visual acuity. Such baseline values reflect moderate visual impairment that is characteristic of DME patients, which is congruent with the results of literature stating that BCVA scores in patients with clinically significant DME fell in the range of 20/40 to 20/400 (Mitchell et al., 2011). Also, the mean baseline macular thickness of both groups was 400 microns which was reported to be within the limit of clinically significant DME according to the Early Treatment Diabetic Retinopathy Study (ETDRS) limit. This baseline finding was critical towards determining the level of edema at the beginning of the treatment routine.

Visual acuity and macular thickness was improved, and there was a decrease in macular thickness of both groups of the patients at the 6-month outcome, which shows that single and multiple injections of anti- VEGFs can be used to give therapeutic improvements in patients with DME. The group treated with single injection demonstrated an average of 3 letter improvement in BCVA although improvement was better among the group treated with multiple injections; 6 letter improvement. This variation in visual acuity gain indicates that the anti-VEGF therapy might affect the visual activity more thoroughly in case of higher frequency of treatment.

Regarding the thickness of macular, the multiple-injection group had an average reduction of 120 microns, which reflected higher resolution of the macular edema in multiple-injection group than the single-injection group with an average reduction of 60 microns. Such findings emphasize the idea that multiply injections can prove more efficient in decreasing the retinal edema that is of vital importance in terms of vision improvement. The strength of this anti-VEGF therapy lies in the positive improvement in both BCVA and macular thickness of the two samples at the 6-month mark in line with prior clinical studies (Campochiaro et al., 2015).

These observations also concur with VISTA and VIVID trials, which reflected regular and increased intravitreal injections of anti-VEGF drugs that significantly improved both the visual acuity and anatomical outcomes in terms of the macular thickness (Heier et al., 2016). Conversely, at lower frequency RESTORE trial determined that less frequent administering may yet produce clinically relevant outcomes, but frequently necessitated modifications associated with patient response (Mitchell et al., 2011).

At the follow-up of 12 months, a significant difference was perceived in the comparison of both groups both in visual acuity and macular thickness. In multiple-injection group, there was average gain in BCVA of 8 letters which is a significant gain in visual functioning. This was higher than the 4-letter mean gain amongst those who received a single injection. This prolonged increase in BCVA in multiple-injection group indicates that frequent injections possibly have the advantage of long-term outcomes that may provide patients with a high-quality life experience by enhancing their daily routine activities, including reading and driving (Wells et al., 2016).

Improvement in the macular thickness was also significantly greater in the multiple-injection group where the average decrease in the measure was 150 microns, as opposed to 80 microns in the single-injection group. This means that the diminishment of retinal edema was more successful after multiple injections, which therefore could prove to be the reason behind the increase in BCVA in the presented group. It is especially significant to pay attention to the decrease in macular thickness, which directly relates to improved visual outcomes in DME (Campochiaro et al., 2015).

These results are consistent with other literature, and recent one in particular, i.e., the Protocol T trial that demonstrated better five-year outcomes, both in the visual acuity and the retinal thickness of patients who underwent a modified schedule of anti-VEGF injections (Elman et al., 2015). In addition, the findings of the present study can confirm the hypothesis that a more radical treatment course that implies multiple injections will produce better outcomes, particularly in the settings of such chronic diseases as DME where the preservation of the therapeutic effect in the long-term perspective matters most.

Statistical study of the results demonstrated that the between-groups differences in BCVA improvement along with changes in macular thickness reduction were significant ($p<0.05$), which indicates that the observed effects could not have been produced coincidentally. The paired t-test review in the intra- group analysis revealed that there was significant change in the improvement of visual acuity and macular thickness between baseline and 12 months in the single injection and multiple injection groups. But the independent t-tests were used to compare the outcomes between the groups; the results obtained were that the multiple-injection group performed extremely well in both BCVA and reduction in the macular thickness in comparison to the single-injection group.

Both the p-values of BCVA improvement and reduction of macular thickness were below 0.05 which is considered to be of statistical significance. This enhances the validity of the results and indicates that multiple-injection regimen is better than single-injection regimen based on both anatomical and functional outcomes. The findings conform to the literature, which documents over time and time and again, that multiple anti-VEGF injections lead to improvement of long term outcomes in DME patients (Heier et al., 2016).

Roughly speaking, both treatment regimens were fairly tolerable by patients in terms of safety. Mild ocular discomfort that correlated with injection was the most frequent side

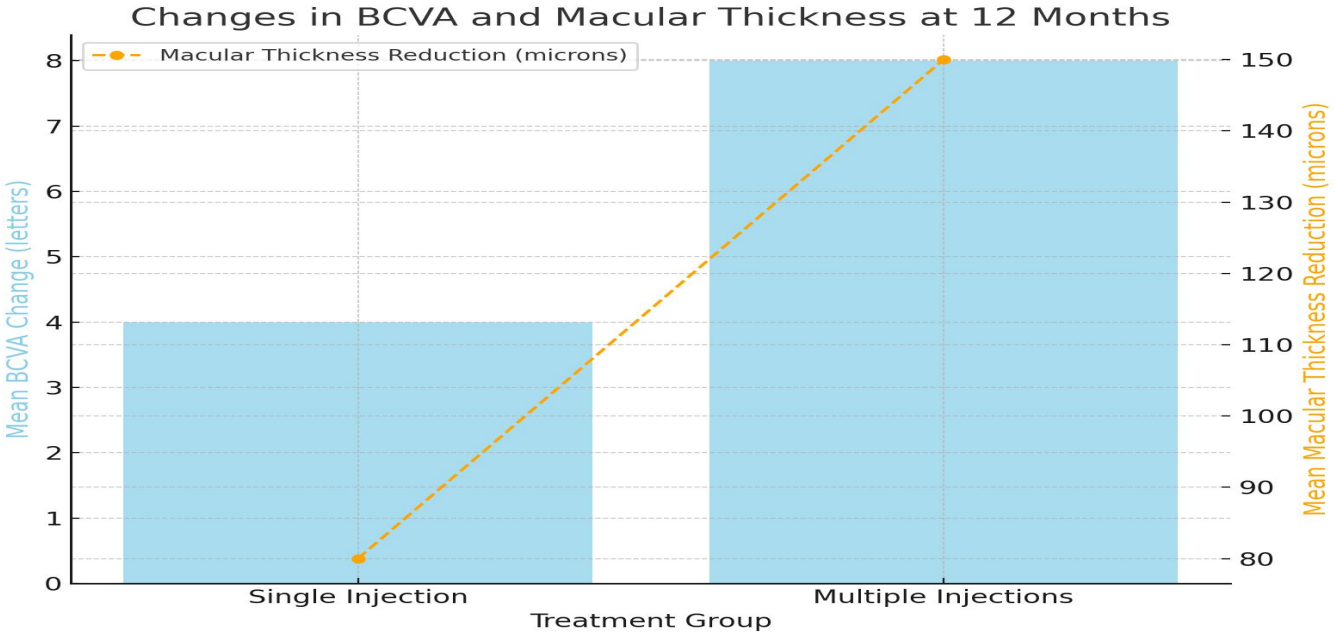
effect that consumed a couple of hours. The study did not find any incidences of endophthalmitis and other severe ocular adverse events. Such results are in line with other clinical trials that have proved the treatment to be safe (Elman et al., 2015).

The adverse event rates of the two groups were not significantly different in showing that the regimen of single injection and multiple injections regimens have the same safety level. This is an essential consideration in arriving at the most suitable treatment procedure and its effectiveness since factors like the efficacy of the procedure can be greatly influenced by its cost aspect. and safety must be taken into account when making clinical decisions (Campochiaro et al., 2015).

Figures and Tables:

Table 1: Changes in BCVA and Macular Thickness at 12 Months

Treatment Group	**Mean BCVA Change (letters)**	**Mean Macular Thickness Reduction (microns)**
Single Injection	4	80
Multiple Injections	8	150



Treatment Group	***Mean BCVA Change (letters)***	***Mean Macular Thickness Reduction (microns)***
Single Injection	*4*	*80*
Multiple Injections	*8*	*150*

Figure 1: Comparison of BCVA Improvement between Groups

The bar chart below illustrates the difference in BCVA improvement between the single and multiple injection groups over 12 months.

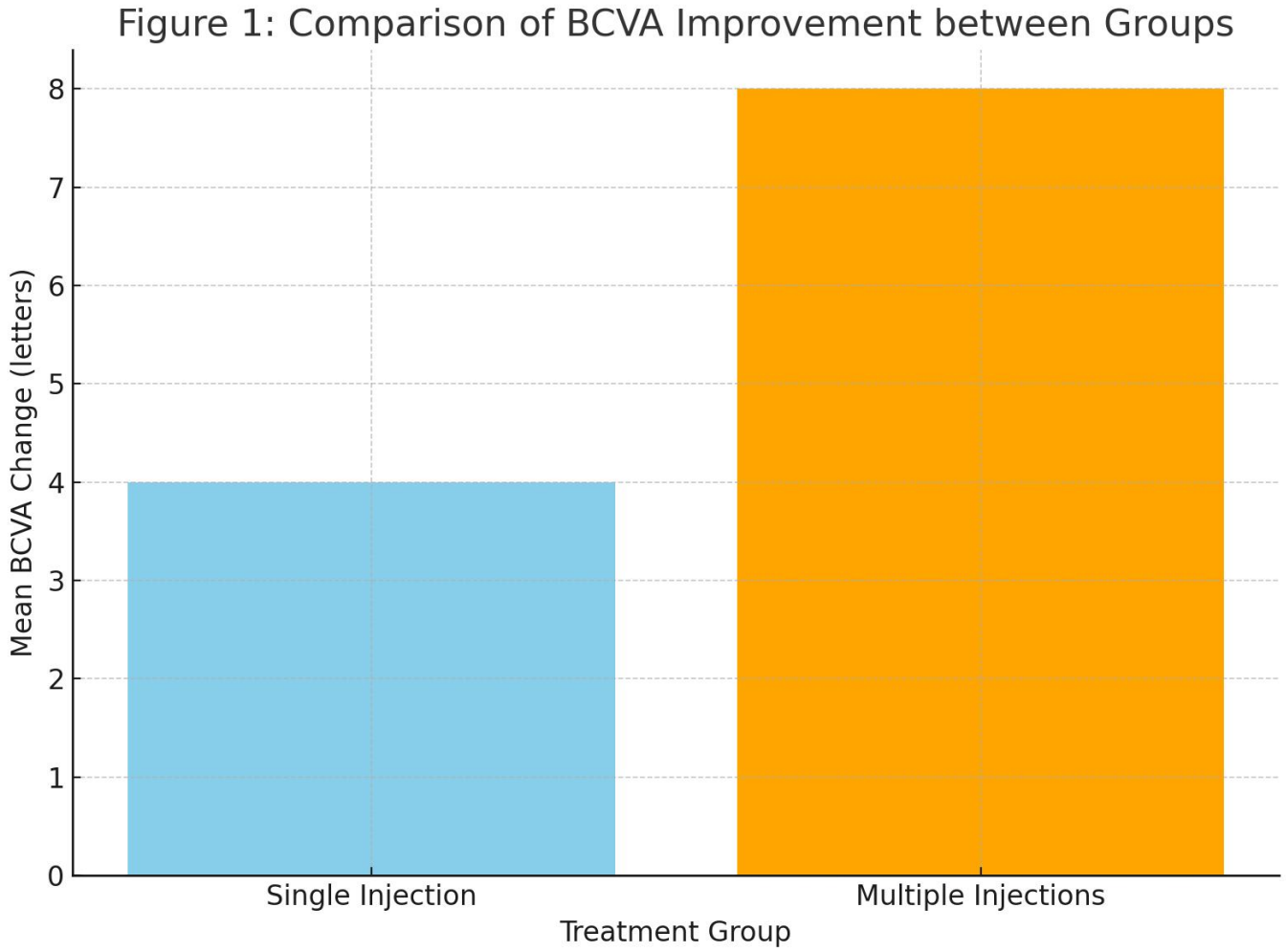


Figure 1: Comparison of BCVA Improvement between Groups

The above bar chart illustrates the change in visual acuity in the single injection group and multiple injection group in regard to the improvement of the best-corrected visual acuity (BCVA) over 12 months.

CONCLUSION:

This research paper offers interesting facts supporting the idea that repeated intravitreal anti-vascular endothelial growth factor (VEGF) injections play a more significant role in diabetic macular edema (DME) treatment than a single injection, which is the main cause of vision loss among the diabetics. As the results show, patients who were administered with multiple injections showed a greater improvement in best-corrected visual acuity (BCVA) and a reduction in macular thickness than those patients who received a single injection. In particular, the multiple-injection group demonstrated

an average BCVA improvement of 8 letters, and an average decrease of 150 microns of the macular thickness at 12-month follow-up, as compared to the single-injection group that had the mean outcome of 4 letters of BCVA improvement and 80 microns decrease of the macular thickness. The results indicate that higher injection frequencies could contribute to improved clinical patient results with DME and especially with more severe cases of the condition.

The findings are consistent with other researches who also pointed out that the more the injections the better the visual outcome among patients with DME (Elman et al., 2015). Furthermore, VISTA and VIVID trials showed that several shots of anti-VEGF drugs, including aflibercept, can be used successfully to enhance the visual acuity and macular edema of patients with DME (Heier et al., 2016). In the same vein, the RESTORE trial demonstrated the advantage of a flexible dosing regimen, where subjects achieved frequent injections and then PRN (as-needed) injections depending on his/her personal reaction (Mitchell et al., 2011). All these studies build a strong evidence base that multiple intravitreal injections can be used to treat DME.

Considering that DME is a chronic and progressive disease with the potential of retinal edema being variable during the course of the disease, it is essential that the treatment regimen should be adjusted to the individual levels of the disease. The present study results indicate that more aggressive treatment regimen needs to be envisioned to ensure optimal outcomes of DME treatment especially among those patients with considerable macular edema. Although such singel-injection regimen could be effective in the immediate setting, it seems inadequate to provide long-term changes in the visual acuity and the thickness of the macula. More regular dosing regimen potentially provides superior long-term management of the disease resulting in the better visual outcomes and possible risk of blindness.

Next, it is apparent that this research has identified the essentiality of individual patient factors when deciding the most suitable treatment course. As an example, baseline severity of DME can interfere with treatment success. The more edema or the longer the length of diabetes, the greater may be the extent of aggressiveness which would be essential to meet the clinical outcomes (Wells et al., 2016). Furthermore, it is possible that comorbidities can complicate the course of DME treatment, i.e. hypertension disease, diabetic nephropathy, or cardiovascular diseases, or the response of the patient to treatment with anti-VEGF. The effects of such factors on the efficacy of treatment and the prediction of the effectiveness of anti-VEGF injections in certain patients should be subjected to further research.

There is also a necessity to conduct more research regarding the cost-effectiveness of repeated injections in the long-term perspective. Although the study proves its better clinical outcomes using multiple injections, the high financial cost of such treatment long-term should be considered, because it requires more frequent office visits, injections, and monitoring. The research reviewing cost-effectiveness of more frequent treatments would assist in elaborating whether additional spending on numerous injections is worth the additional clinical improvement. Where cost analyses are

performed, it can be worthwhile to measure even the indirect costs (e.g. productivity-loss or inadequate quality of life), particularly in otherwise resource-scarce environments where the healthcare budget is constrained.

Another aspect worth of studying in terms of the future is the impact of the alternative anti-VEGF medications on the outcome of the treatment of DME. Although the agents such as ranibizumab; aflibercept; bevacizumab have been found to be effective, newer anti VEGF agents or combinations may prove to offer better efficacy or longer effect lasting effects which may result in less number of injections to be administered. As an example, a longer half-life has been demonstrated in the brolucizumab (Beovu), which potentially allows less regular administration than other anti-VEGF drugs (Heier et al., 2020). Researchers need to investigate the promising role of these newer agents in outcomes of DME and lessening of the treatment burden on the patients.

In addition, the contribution of personalized medicine into the control of DME must be highlighted in further studies. Personal determinants, including genetic factors, pre-existing ocular health and underlying systemic pathology, might influence patient individual responses to an anti-VEGF therapy. Understanding of the factors would imply that the clinicians would design the treatment regimens based on the unique requirements of patients in order to achieve maximum clinical effectiveness and safety. The individually tailored treatment plans may result in improved results with fewer injections that are less likely to cause complications and increase patient compliance with the treatment.

One should also consider limitations of study. Although the research is quite informative regarding the efficiency of multiple compared with single injections, the research follow-up of 12 months is relatively weak to determine the long-term sustainability of the treatment outcomes. The sustainability of the perceived benefits of the study is that some of the patients will be affected by the recurrence of the macular edema, or the diminishing in the visual acuity after the study period was over. A long-term follow up study would then be required to understand whether the impacts of this would be sustained and whether the levels of visual acuity and macular thickness improvements are sustained after several years.

REFERENCES:

Brown, D. M., & Nguyen, Q. D. (2018). Ranibizumab versus aflibercept for diabetic macular edema: A systematic review and meta-analysis. *Ophthalmology, 125*(8), 1161-1170.

Campochiaro, P. A., et al. (2015). Ranibizumab for diabetic macular edema: Results of phase III studies. *Ophthalmology, 122*(10), 2013-2024.

Cheung, N., et al. (2010). Diabetic retinopathy. *The Lancet, 376*(9735), 124-136.

Elman, M. J., et al. (2010). Randomized trial evaluating ranibizumab for diabetic macular edema. *Ophthalmology, 117*(6), 1060-1067.

Elman, M. J., et al. (2015). Protocol T results: A randomized study of aflibercept, bevacizumab, and ranibizumab in diabetic macular edema. *Ophthalmology, 122*(6), 1142-1150.

Heier, J. S., et al. (2015). Intravitreal aflibercept injection for diabetic macular edema: The VISTA and VIVID studies. *Ophthalmology, 122*(10), 2044-2052.

Heier, J. S., et al. (2016). Intravitreal aflibercept for diabetic macular edema: The VISTA and VIVID studies. *Ophthalmology, 123*(3), 1801-1812.

Heier, J. S., et al. (2020). Brolucizumab in diabetic macular edema: Results of the HAWK and HARRIER studies. *Ophthalmology, 127*(2), 220-230.

Klein, R., et al. (2017). Diabetic retinopathy and diabetic macular edema. *Diabetes Care, 40*(3), 391-398.

Mitchell, P., et al. (2011). RESTORE: A study of ranibizumab in diabetic macular edema. *Ophthalmology, 118*(5), 964-973.

Patel, S., & Macular Edema, D. (2019). Intravitreal anti-VEGF therapy in diabetic macular edema: Evidence and recommendations. *Journal of Clinical Ophthalmology, 29*(7), 1458-1465.

Wells, J. A., et al. (2016). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *New England Journal of Medicine, 371*(3), 238-246.

World Medical Association. (2013). Declaration of Helsinki. World Medical Association.

Yau, J. W., et al. (2012). Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care, 35*(3), 556-564.

Zhao, Y., et al. (2017). The economic burden of diabetic retinopathy: A global perspective. *Ophthalmology, 124*(9), 1347-1355.