

Comparative Study between Effects of Intravitreal Injection of Ranibizumab With and Without Anterior Chamber Paracentesis in Diabetic Macular Oedema

AHMED A. ELBARAWY, F.R.C.S., M.D.; SHIMAA H. ALI, M.Sc.; MAHMOUD A. ALI, M.D. and AHMED F. GABR, FRCSEd, M.D.

The Department of Ophthalmology, Faculty of Medicine, Aswan University

Abstract

Background: Diabetic macular edema (DME) is a common and disabling eye condition. Despite the fact that DME is a sight-threatening condition, it is also one of the most treatable. Intravitreal injection of anti-vascular endothelial growth factors (VEGFs) has emerged as the gold standard first-line treatment for DME in recent years.

Aim of Study: This study compared the effects of intravitreal injection of ranibizumab with and without anterior chamber (AC) paracentesis.

Patients and Methods: A single center comparative study enrolled 90 patients with DME. Those patients were randomly divided into two groups; 45 patients underwent intravitreal injection with ranibizumab preceded by anterior chamber paracentesis (group A). The other 45 patients underwent intravitreal injection with ranibizumab without anterior chamber paracentesis (group B). Both groups were studied preoperatively and one day, one week, one month and three months post operatively regarding visual acuity, intraocular pressure (IOP), macular thickness and peripapillary retinal nerve fiber layer (RNFL) thickness.

Results: The post-operative changes in visual acuity, central, average and peripapillary RNFL thickness was statistically insignificant between the two groups. However, group A (though not statistically significant) achieved higher visual acuity, lower macular thickness and better peripapillary RNFL thickness while IOP measurements were significantly higher in group B through out the follow-up period of the study.

Conclusion: Both techniques gave excellent post-operative results regarding visual acuity, central and average macular thickness but those patients underwent paracentesis of AC had better peripapillary RNFL thickness and IOP.

Key Words: Diabetic macular edema, ranibizumab – Visual acuity– Intraocular pressure – Retinal nerve fiber layer.

Introduction

THE most frequent cause of visual loss in people with diabetic retinopathy is diabetic macular edema (DME) [1].

Correspondence to: Dr. Shimaa H. Ali, The Department of Ophthalmology, Faculty of Medicine, Aswan University

Anti-vascular endothelial growth factor (anti-VEGF) agents have recently been shown to be superior to laser therapy in the treatment of DME with the center involvement [2].

Intravitreal ranibizumab has been shown to be a valuable treatment for DME. It promotes significant improvement in uncorrected and BCVA, reducing the risk of further vision loss with low rates of local or systemic side effects [3].

Intravitreal injection causes increase of intraocular pressure (IOP) immediately leading to pressure spikes that tends to be high and transient. There is no consensus regarding the effect and for how long IOP should be monitored after the injections [4].

This study aimed to determine visual and anatomical effects of intravitreal injection of ranibizumab when combined with anterior chamber paracentesis in patients with DME.

Patients and Methods

This single-center comparative interventional study was performed from December 2020 to June 2022 at Aswan University Hospital. Informed consent was obtained by all patients after full explanation about the procedure. Approval for the study was obtained from the local Ethical Committee with all study steps was done in accordance with the Declaration of Helsinki.

Sample size:

Sample size was estimated using G*Power 3 software. Ninety (90) patients with diabetic macular edema were enrolled divided into two groups: group (A) included 45 patients; underwent intravitreal injection of ranibizumab with anterior chamber paracentesis and group (B) included 45 patients; underwent intravitreal injection of ranibizumab without anterior chamber paracentesis.

Selection criteria:

Patients who were above the age of 40 years old with non-proliferative diabetic retinopathy and average macular thickness (AMT) 300-500 μm were eligible for the study. Exclusion criteria included; proliferative diabetic retinopathy, history of anti-glaucoma medications, patients diagnosed with glaucoma or glaucoma suspects and patients with history of injection of anti-VEGF since the past six months. Also patients with history of usage of systemic or topical steroids, focal macular laser treatment, intraocular surgery in the past six months or previous vitreo retinal surgery.

Methods:

Detailed ocular and medical history was taken followed by detailed ocular examination that included uncorrected and best corrected visual acuity using decimal notation, Slit-lamp examination for anterior segment and biomicroscopy using Volk 78D fundus. Intraocular pressure (IOP) was assessed using Goldman's applanation tonometry. Central (CMT) and average macular thicknesses as well as peripapillary retinal nerve fiber layer thickness were evaluated using optical coherence tomography (OCT) (Topcon 3D-OCT-2000 (FAPlus), (Tokyo, Japan). CMT denoted thickness at the point of intersection of the six radial scans of the OCT, whereas AMT represented thickness in the central one mm diameter area of the macula.

Intraoperative procedure:

For both study groups injections were performed in the operating room following routine aseptic technique. Under topical anesthesia intravitreal ranibizumab (LucentisTM, Genetech, South San Francisco, CA) was injected using a 29 G needle. Anterior chamber paracentesis was performed just after the injections in group (A) using 1-ml plastic syringe with a 29-gaugeneedle to obtain 0.2ml of aqueous humor.

Postoperative evaluation and follow-up:

Followed-up of patients was done one day, one week, one month and three months post injection. At each visit, patients underwent slit lamp examination, unaided visual acuity, BCVA and IOP measurement. At the end of the first and the third month of injection peripapillary RNFL, average and central macular thickness were measured by OCT.

Statistical analysis:

Data analysis was done using SPSS (Statistical package for social sciences) version 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Data were described in the form of frequencies, percentages, mean,

standard deviations, median and interquartile ranges. Independent sample *t*-test was used to test the difference between two groups concerning numerical variables. Repeated measures ANOVA was used to test the association between paired numerical data if were more than two groups and normally distributed. Chi square test to test the association between categorical variables. Level of confidence was kept at 95% and hence, *p*-value was considered significant if <0.05 .

Results

Demographic data of patients in both study groups was illustrated in Table (1) with no significant difference regarding age and duration of diabetes. Low significance female predominance was realized among patients in group B (p 0.049).

Table (1): Demographic data of the studied groups.

Variable	Group A (n=45)	Group B (n=45)	<i>p</i> -value
Age	58.02±9.67	55.78±17.16	0.447*
<i>Gender:</i>			
Male	21 (46.7)	12 (26.7)	0.049**
Female	24 (53.3)	33 (73.3)	
Duration of diabetes	12.16±4.82	12.73±7.87	0.680*

**t*-test. **Chi-square test.

Compared to baseline, significant improvement in the mean visual acuity was noted by the end of first and third months in both groups ($p < 0.001$). No further improvement of mean BCVA could be found after one month till the end of follow-up (p 0.564 and 0.076 respectively) (Fig. 1).

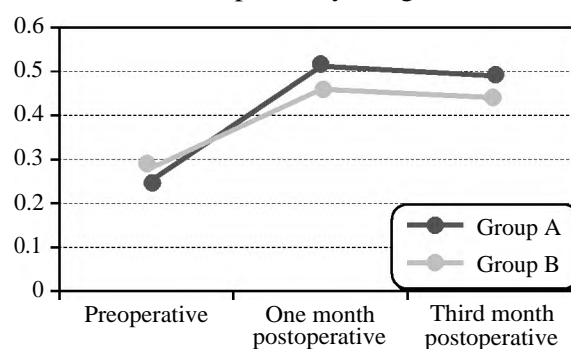


Fig. (1): Best corrected visual acuity among studied groups.

Preoperatively, there was no significant difference in IOP between both study groups. While one day, one week, one month and three months postoperative IOP was higher among patients in group B when compared to paracentesis group (*p* value 0.021, 0.034, <0.001 and 0.163 respectively). When analyzing patients in group A and group B there was significant decrease in IOP over follow-up period (p 0.002 and <0.001 respectively) (Fig. 2).

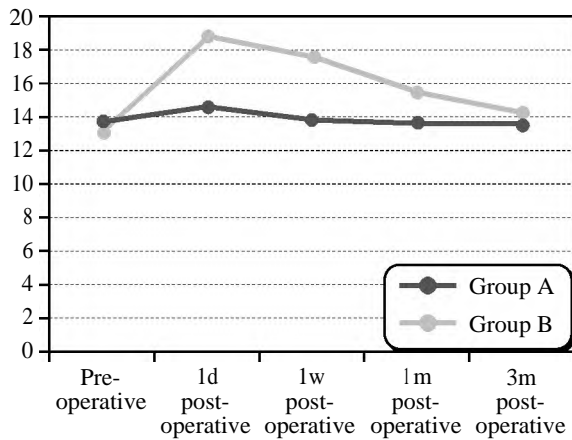


Fig. (2): Intraocular pressure among studied groups.

Comparison between both groups concerning assessment of central macular thickness (CMT) revealed significantly higher baseline thickness in group A ($p=0.014$). One month and three months postoperatively patients within group A had insig-

nificant difference in CMT when compared to group B (p -value equal 0.380 and 0.319 respectively). Analysis of CMT over follow-up period revealed significant reduction in both study groups compared to baseline levels ($p<0.001$). Compared to first month, no further improvement in CMT could be detected by the end of third month in both study groups (Table 2), (Fig. 3).

As regards average macular thickness (AMT) no significant difference was found between both groups ($p=0.170$). One month and three months postoperatively patients within group A had a slightly lower AMT when compared to group B (p 0.333 and 0.332 respectively). Analysis over follow-up period revealed significant reduction of AMT in both study groups compared to baseline levels ($p<0.001$). Compared to first month, mild increase in AMT was detected by the end of third month in both study groups ($p<0.001$ and 0.002 respectively) (Table 2), (Fig. 4).

Table (2): Central macular thickness and average macular thickness in the studied groups.

	Group A (n=45) Mean ± SD	Group B (n=45) Mean ± SD	p -value*
Central macular thickness:			
Preoperative	371.33±60.46	331.22±77.7	0.014
1 month postoperative	288.07±55.51	277.02±62.06	0.380
3 month postoperative	288.73±56.49	276.36±59.17	0.319
With in group difference	<0.001 <0.001 ^a , <0.001 ^b , 1.00 ^c	<0.001 <0.001 ^a , <0.001 ^b , 1.00 ^c	
Average macular thickness:			
Preoperative	331.13±37.52	319.17±42.05	0.170
1 month postoperative	294.4±26.88	300.19±35.34	0.333
3 month postoperative	296.3±26.6	302.49±35.37	0.322
With in group difference	<0.001 <0.001 ^a , <0.001 ^b , <0.001 ^c	<0.001 <0.001 ^a , <0.001 ^b , 0.002 ^c	

*Independent sample t -test.
 p -value was significant if <0.05 .

a: Preoperative Vs. one month postoperative.
b: Preoperative Vs. three months postoperative.
c: One month Vs. three months postoperative.

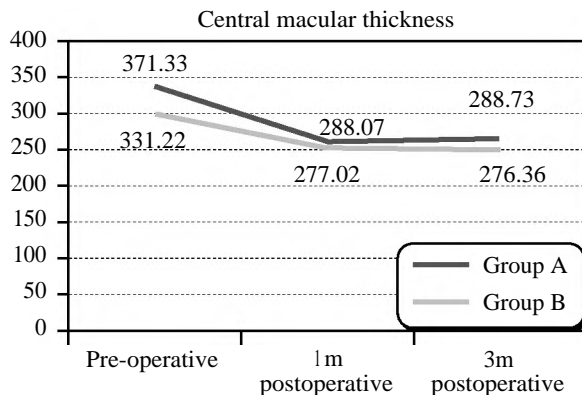


Fig. (3): Central macular thickness among studied groups.

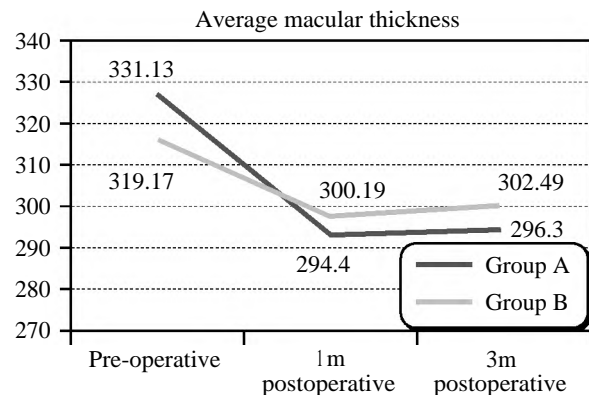


Fig. (4): Average macular thickness among studied groups.

Comparison between both groups concerning assessment of total retinal nerve fiber layer thickness (RNFL) revealed no significant difference between both study groups preoperatively as well as at one and three months postoperatively (p 0.415, 0.184 and 0.172 respectively). Analysis of total nerve fiber thickness over follow-up period dem-

onstrated significant decrease of thickness in both study groups more in group B (p -value equal 0.012 and <0.001 respectively) (Table 3).

No complications related to intravitreal injection or to anterior chamber paracentesis were encountered in the both study groups.

Table (3): Total retinalnerve fiberlayer thickness (Tot-RNFL) in the studied groups.

Tot-RNFL thickness	Group A (n=45)	Group B (n=45)	p -value*
Preoperative	99.4± 10.34	97.47±7.55	0.415
One month Postoperative	99.11± 10.27	96.27±7.25	0.184
Three months Postoperative	98.89± 10.21	96.02±7.09	0.172
With in group difference	0.012	<0.001	
	0.403 a , <0.001 b , <0.001 c	<0.001 a , <0.001 b , 0.004 c	

*Independent sample t -test.

p -value was significant if <0.05 .

a: Preoperative Vs. one month postoperative.

b: Preoperative Vs. three months postoperative.

c: One month Vs. three months postoperative.

Discussion

Diabetic macular edema (DME) is a common manifestation of diabetic retinopathy and it is the most common cause of vision loss in diabetic retinopathy [5]. Intravitreal injections of anti-VEGF antibodies significantly improved functional as well as anatomical results in diabetic macular edema with risk of rise of IOP with its consequences [6]. Ninety patients were included in the current study to illustrate the impact of combination of paracentesis to intravitreal injection on functional and anatomical parameters in cases of macular edema.

This study revealed improvement in the functional results (BCVA) in both groups. It also revealed that the mean BCVA in group A were slightly higher (though not statistically significant) compared to group B in the earlier follow-up phase. However, by the end of the study functional results were almost the same in both groups. The reported improvement of visual acuity following intravitreal injection of ranibizumab had no association with anterior chamber paracentesis.

Virgili et al., [5] in meta-analysis concluded that anti-VEGF drugs are effective at improving vision in people with DME with 30-40% of patients were likely to experience an improvement of three or more lines of visual acuity at one year.

This study revealed increase in the intraocular pressure (IOP) after intravitreal injection of ranibi-

zumab in both groups. After initial spike, the level of IOP gradually decreased. However there was statistically significant decrease in the IOP in paracentesis group in comparison to group B throughout the time of the study.

In line with these findings, previous study found that IOP variation was statistically significant between pre- and postoperative measurements. The authors stated that more than one third of the eyes achieved IOP >30 mm Hg 5 minutes after injection [7].

Other studies suggested that late, sustained and cumulative IOP elevation was estimated between 2.1 % and 13 % after repeated injections of anti-VEGF [8] Choiet al., [9].

Also reported that 9.4% of patients who received intravitreal injection of anti-vascular endothelial growth factor agents developed elevated IOP >25 mmHg and 58.3% of them developed sustained elevated IOP. But, they reported that elevated IOP had no association with injection frequency, number of injections, or type of anti-VEGF used.

Several studies demonstrated the effectiveness of prophylactic AC paracentesis in prevention of immediate or long-term IOP rise associated with intravitreal injections [10-13]. Moreover, Other investigator s concluded that anterior chamber paracentesis may offer a comfortable, effective ,and less pain fulalternative to avoid acute IOP rise after injection, especially in patients with small

anterior chambers, small vitreous volumes, with a history of multiple injections, and in patients with advanced glaucomatous optic neuropathy [14,15].

The present study also demonstrated that the central and average macular thickness decreased throughout the time of the study in both groups. Group A achieved nearly the same reduction of the central and average macular thickness as group B that persisted until the end of the follow-up time.

The improvement in CMT and AMT in both groups after intravitreal ranibizumab injection could be due to its effect on inhibiting upregulated VEGF, which has been linked to the pathogenesis of DME. Several studies have shown that anti-VEGF injections are effective in improving DME [5,16,17].

Total retinal nerve fiber layer (RNFL) thickness was found to be insignificantly reduced in all quadrants throughout the time of the study in both groups, but group B had more reduction than group A that persist until the end of the follow-up time. Soheilian et al., [18].

Concluded that anterior chamber paracentesis prevents peripapillary RNFL loss [15]. In a meta-analysis revealed that average RNFL thickness following repeated anti-VEGF injections was not significantly different from baseline and concluded that there was no association between anti-VEGF injections and RNFL thickness changes when all studies were examined together.

The present study experienced no complications related to anterior chamber paracentesis. Similar safety profile of anterior chamber paracentesis was reported by some investigators [19]. When caution is exercised, the incidence of complications related to anterior chamber paracentesis may be low, according to Saxena et al., [20]. Pain, traumatic iris injuries, hyphema, severe inflammation, persistent leakage with hypotony as well as endophthalmitis are among reported complications associated with anterior chamber paracentesis [18].

The main limitations of the current study included relatively small sample size, short term follow of those cases as well as lack of visual field testing to confirm whether retinal nerve fiber defect is associated with functional loss or not. It is recommended to implement similar study on large scale of patients for longer duration of follow-up using perimetry to confirm the present findings.

In conclusion, intravitreal injection of ranibizumab improves visual acuity and reduces central

and average macular thickness in both study groups. Temporary rise of IOP and reduction of retinal nerve fiber thickness were less noticeable when combined with anterior segment paracentesis.

Fund: No.

Conflict of interest.

References

- 1- KIM E.J., LIN W.V., RODRIGUEZ S.M., et al.: Treatment of diabetic macular edema. *Curr. Diab. Rep.*, 19 (9): 68, 2019.
- 2- CHEN Y.P., WU A.L., CHUANG C.C., et al.: Factors influencing clinical outcomes in patients with diabetic macular edema treated with intravitrealranibizumab: Comparison between responder and non-responder cases. *Sci. Rep.*, 9 (1): 1-8, 2019.
- 3- ZUCCHIATTI I. and BANDELLO F.: Intravitreal ranibizumab in diabetic macular edema: Long-term outcomes. *Management of Diabetic Retinopathy*, 60: p. 63-70, 2017.
- 4- CARNOTA-MÉNDEZ P., MÉNDEZ-VÁZQUEZ C. and OTERO-VILLAR J.: Effect of prophylactic medication and influence of vitreous reflux inpressure rise after intravitreal injections of anti-VEGF drugs. *Eur. J. Ophthalmol.*, 24 (5): 771-777, 2014.
- 5- VIRGILI G., PARRAVANO M. and EVANS J.R.: Anti-vascular endothelial growth factor for diabetic macular oedema: A network meta-analysis. *Cochrane Database Syst. Rev.*, 6 (6): CD007419, 2017.
- 6- SHIMIZU N., OSHITARI T., TATSUMI T., et al.: Comparisons of Efficacy of Intravitreal Aflibercept and Ranibizumab in Eyes with Diabetic Macular Edema. *Biomed Res. Int.*, 2017: 1747108, 2017.
- 7- LEMOS V., CABUGUEIRA A., NORONHA M., et al.: Intraocular Pressure in Eyes Receiving Intravitreal Anti-vascular Endothelial Growth Factor Injections. *Ophthalmologica*, 233 (3-4): 162-168, 2015.
- 8- LELEU I., PENAUD B., BLUMEN-OHANA E., et al.: Late and sustained intraocular pressure elevation related to intravitreal anti-VEGF injections: Cases requiring filteringsurgery. *J. fr. Ophthalmol.*, 41 (8): e329-e340, 2018.
- 9- CHOI D.Y., ORTUBE M.C., MCCANNEL C.A., et al.: Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib. *Retina*, 6: 1028-1035, 2011.
- 10- JEONG S., SAGONG M. and CHANG W.: Acute angle closure attack after an intravitreal bevacizumab injection for branch retinal veinocclusion: A case report. *BMC Ophthalmol.*, 17 (1): 25, 2017.
- 11- HILLIER R.J., OJAIMI E., WONG D.T., et al.: Aqueous humor cytokine levels and anatomic response to intravitreal ranibizumab in diabetic macular edema. *JAMA Ophthalmol.*, 136 (4): 382-388, 2018.
- 12- SATO T., TAKEUCHI M., KARASAWA Y., et al.: Intraocular inflammatory cytokines in patients with neovascular age-related macular degeneration before and after initiation of intravitreal injection of anti-VEGF inhibitor. *Sci. Rep.*, 8 (1): 1-10, 2018.

- 13- HOGUET A., CHEN P.P., JUNK A.K., et al.: The effect of anti-vascular endothelial growth factor agents on intraocular pressure and glaucoma: A report by the American Academy of Ophthalmology. *Ophthalmology*, 126 (4): 611-622, 2019.
- 14- KARAKAHYA R.H.: Anterior Chamber Paracentesis Offers a Less Painful Experience During Intravitreal Anti-vascular Endothelial Growth Factor Administration: An Intra individual Study. *Cureus*, 13 (11): e20051, 2021.
- 15- SOHEILIAN M., KARIMI S., MONTAHAE T., et al.: Effects of intravitreal injection of bevacizumab with or without anterior chamber paracentesis on intraocular pressure and peripapillary retinal nerve fiber layer thickness: A prospective study. *Graefe's Arch. Clin. Exp. Ophthalmol.*, 255 (9): 1705-1712, 2017.
- 16- NGUYEN Q.D., BROWN D.M., MARCUS D.M., et al.: RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: Results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*, 119 (4): 789-801, 2012.
- 17- BRESSLER N.M., VARMA R., SUÑER I.J., et al.: RIDE and RISE Research Groups. Vision- related function after ranibizumab treatment for diabetic macul results from RIDE and RISE. *Ophthalmology*, 121 (12): 2461-2472, 2014.
- 18- SAHNI J., PATEL S.S., DUGEL P.U., et al.: Simultaneous inhibition of angiotensin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. *Ophthalmology*, 126 (8): 1155-1170, 2019.
- 19- BACH A., FILIPOWICZ A., GOLD A.S., et al.: Paracentesis following intravitreal drug injections in maintaining physiologic ocular perfusion pressure. *Int. J. Ophthalmol.*, 10 (12): 1925-1927, 2017.
- 20- SAXENA S., LAI T.Y., KOIZUMI H., et al.: Anterior chamber paracentesis during intravitreal injections in observational trials: Effectiveness and safety and effects. *Int. J. Retina and Vitreous*, 5 (1): 1-5, 2019.

دراسة مقارنة بين تأثيرات الحقن داخل الجسم الزجاجي لعقار رانيببوزوماب مع أو بدون بزل الغرفة الأمامية فى الوذمة البقعية نتيجة مرض السكرى

تعد الوذمة البقعية السكرية مظهر شائع لاعتلال الشبكية السكرى حيث تزداد سماكة الشبكية فى البقعة مما يسبب فقدان تدريجى للرؤية المركزية.

وقد أثبتت العديد من التجارب السريرية أن حقن عقار رانيببوزوماب داخل الجسم الزجاجى علاج قيم للوذمة البقعية السكرية مما يعزز تحسناً ملحوظاً فى حدة البصر. تهدف هذه الدراسة لمقارنة تأثير الحقن داخل الجسم الزجاجى لعقار رانيببوزوماب مع أو بدون بزل الغرفة الأمامية على حدة الإبصار وضغط العين وسمك طبقة الألياف العصبية الشبكية حول حليلة العصب البصرى وسمك البقعة الشبكية فى المرضى الذين يعانون من الوذمة البقعية السكرية.

تكونت الدراسة من تسعين مريضاً تم تقسيمهم إلى مجموعتين :

المجموعة الأولى تكونت من خمس وأربعون مريض تم حقن عقار رانيببوزوماب داخل الجسم الزجاجى مع بزل الغرفة الأمامية لهم والمجموعة الثانية تكونت من خمس وأربعون مريض تم حقن عقار رانيببوزوماب لهم بدون بزل الغرفة الأمامية. وقد تم إجراء فحص شامل لجميع المرضى بما فيهم حده الإبصار وقياس ضغط العين وسمك البقعة الشبكية وسمك طبقة الألياف العصبية الشبكية حول حليلة العصب البصرى.

تم تقييم النتائج عند مرور يوم وأسبوع وشهر وثلاث أشهر من تاريخ إجراء الحقن.

كانت نسبة النجاح للمجموعتين بعد متابعة لمدة ثلاث أشهر متساوية. حيث تم ملاحظة تحسن ملحوظ فى حده الإبصار وسمك البقعة الشبكية للمجموعتين كما أثبتت الدراسة أن قياسات ضغط العين كانت أعلى فى المجموعة الثانية مقارنة بالمجموعة الأولى خلال فترة المتابعة وبمقارنة التغيرات التى طرأت على سمك طبقة الألياف العصبية الشبكية حول حليلة العصب البصرى بعد إجراء الحقن فى المجموعتين لم تكن كبيرة إحصائياً ولكن فقد فى سمك تلك الطبقة كان أعلى فى المجموعة الثانية.

خلال هذه الدراسة فأنا ننصح بإجراء بزل للغرفة الأمامية للعين قبل إجراء حقن عقار رانيببوزوماب داخل الجسم الزجاجى نظراً للنتائج التى حصلنا عليها لهذه الطريقة على ضغط العين وحفاظها على طبقة الألياف العصبية الشبكية حول حليلة العصب البصرى.