The Effect of Acute Rises in Intraocular Pressure after Intravitreal Bevacizumab Injection on the Peripapillary Retinal Nerve Fiber Layer Thickness and the Role of Anterior Chamber Paracentesis

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Abstract

Purpose: To evaluate acute changes in intraocular pressure (IOP) and their short-term effects on the peripapillary retinal nerve fiber layer (RNFL) thickness after intravitreal bevacizumab (IVB) injection.

Methods: Fifty-eight eyes of 37 patients with treatment-naïve diabetic macular edema or exudative age-related macular degeneration were included in the study. Patients were divided into two groups, and the participants of each group received 3 monthly injections of IVB. IOP was measured right before the injection, immediately after the injection, and 5 min and 20 min after each injection. Peripapillary, RNFL thickness was measured before the injection and 1 month after the third injection. In the second group, anterior chamber (AC) paracentesis was performed before IVB injection.

Results: IOP values after injection in all sessions were significantly higher in the first group ($P < 0.001$). The peripapillary RNFL thickness changes 1 month after the third injection was not statistically significantly different in each group ($P = 0.816$ and 0.773 for the first and second groups, respectively).

Conclusion: AC paracentesis is an effective modality to reduce the acute rise in IOP. The effect of acute IOP elevation on the peripapillary RNFL thickness was not statistically significant.

Keywords: Anterior chamber paracentesis, Intraocular pressure, Intravitreal bevacizumab, Peripapillary retinal nerve fiber layer

INTRODUCTION

Diabetic retinopathy and age-related macular degeneration are among the most prevalent causes of blindness in adults. The standard treatment of diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) is intravitreal anti-vascular endothelial growth factor (VEGF) injection.[1] Due to the chronic nature of DME and nAMD, the most standard treatment regimens recommend multiple intravitreal anti-VEGF injections at least during the 1st year of treatment. One of the concerns in this regard is rising intraocular pressure (IOP) with the subsequent risk of glaucomatous optic nerve head (ONH) damage. These issues have been evaluated in several studies, but the results have been inconclusive, and the significance of the matter remains to be elucidated. Several hypotheses have been proposed to explain the acute IOP spike after intravitreal injections,

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including anterior chamber (AC) angle narrowing, trabecular meshwork contracture (which results in reduced outflow facility), trabecular clogging with large molecules and proteins, decreased intraocular nitrite oxide, and intraocular hydrostatic pressure elevation secondary to volume excess.[1-3] To avoid acute IOP increases, authors have made several recommendations, including using AC paracentesis (the most effective method), pretreatment with anti-glaucoma medications, and ocular decompression (with a cotton-tipped applicator before intravitreal injection).[1,4] However, the exact role of the AC paracentesis in preventing glaucomatous damages following intravitreal injection is not clear. Furthermore, it is an invasive procedure that is associated with complications such as traumatic cataract and endophthalmitis.[4,5] Therefore, there is no consensus on this intervention for all patients who have undergone intravitreal anti-VEGF injection. In this study, we aimed to evaluate the effect of AC paracentesis on the IOP rise and peripapillary short-term retinal nerve fiber layer (RNFL) thickness changes following intravitreal injection to add more evidence to the literature.

METHODS

All procedures performed in the studies involving human participants followed the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Furthermore, all procedures were approved by the institutional review board committee of Tehran University of Medical Sciences (Ethical code: IR.TUMS.FARABIH.REC.1396.4334). Informed consent was obtained from all participants.

In this study, patients with treatment-naïve DME without proliferative diabetic retinopathy (PDR) and treatment-naïve nAMD were included in the study. Exclusion criteria were defined as a history of intravitreal injection, laser retinal photocoagulation, PDR, glaucoma disease, and severe media opacity. Patients were randomly assigned to Group A or Group B. Group A patients received only 1.25-mg intravitreal bevacizumab (IVB) injection. For patients in Group B, the intravitreal injection was preceded by AC paracentesis. All patients received 3 monthly injections. In each session, IOP was measured with Tonopen (Reichert, Depew, NY) with the patient in the supine position (i) right before injection, (ii) immediately after the injection, (iii) 5 min after the injection, and (iv) 20 min after the injection. Ocu-Film covers were sterilized with gas plasma technique and replaced for each IOP measurement.

For all the participants, the peripapillary RNFL thickness was measured using spectral-domain optical coherence tomography (SD-OCT) (Spectralis SD-OCT, Heidelberg Engineering, Germany) at the baseline and month 3 (1 month after the third IVB injection) with follow-up software available in the device. The peripapillary RNFL (particularly the temporal region may be affected by the wax and wane nature of macular edema) and on the other hand glaucoma has a propensity to damage inferotemporal and supratemporal

more than other sectors. Therefore, we recorded the data of peripapillary sectors separately for further analysis.

All statistical analyses were performed by Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC.). To compare the changes in RNFL values within the groups, we used a paired *t*-test with estimates of fixed effects. To compare the IOP values within the groups in each session, we used a repeated measure analysis with estimated marginal means. Comparison of the IOP between the two groups, adjusted for the baseline values, through the sessions was performed through a multilevel linear regression analysis with 4 levels (single measurements, each time, each session, each subject, and correspondingly form level 1 to level 4). Furthermore, the comparison of the baseline values was performed in this analysis. $P < 0.05$ were considered statistically significant.

RESULTS

Fifty-eight eyes of 37 patients (30 eyes from Group A and 28 eyes from Group B) were included in the study. The mean age of the patients was 62.9 ± 10 years, and the median age was 64 years (range, 34–82 year). Sixteen (43.3%) patients were male, and 21 (56.8%) were female. Of the 58 eyes, 10 (17.2%) had nAMD, and 48 (82.8%) had DME. The baseline means pre-IOP values were 15 ± 3 and 16 ± 3 mmHg in Group A and Group B, respectively, during the first session. This difference was not statistically significant ($P = 0.233$). Mean immediate post-IOP, 5 min IOP, and 20 min IOP values were 37 ± 8, 31 ± 9, and 24 ± 7 mmHg, respectively, for Group A and 19 ± 5, 14 ± 3, and 14 ± 3 mmHg for Group B. The values of all postinjection measurements were significantly lower in Group B ($P < 0.001$ for all measurements).

A similar finding was observed for the second and third injections [Figure 1]. In Group A, the 20 min IOP values remained significantly higher than pre-IOP measurements for all sessions (mean differences from the baseline for the first, second, and third sessions were 8.667, 10.700, and 9.567, respectively, ($P < 0.001$ for all sessions). In contrast, 20 min IOP was not significantly different from pre-IOP measurements for Group B for the first ($P = 0.060$) and third ($P = 0.162$) sessions. However, the 20 min IOP was significantly lower than that of the pre-IOP measurement for the second session ($P = 0.041$).

The mean global peripapillary RNFL thicknesses before and after treatment in Group A were 110 ± 19 and 111 ± 18 μ, respectively. The changes were not statistically significant ($P = 0.816$). A similar finding was evident in Group B (115 ± 19 μ, $P = 0.773$). Furthermore, the peripapillary RNFL thicknesses in the temporal superior, temporal inferior, nasal superior, and nasal inferior sectors at month 3 were not significantly different in either group when compared to the baseline values [Table 1]. Likewise, changes in the mean peripapillary RNFL thickness from the baseline values were not statistically significant between the two groups
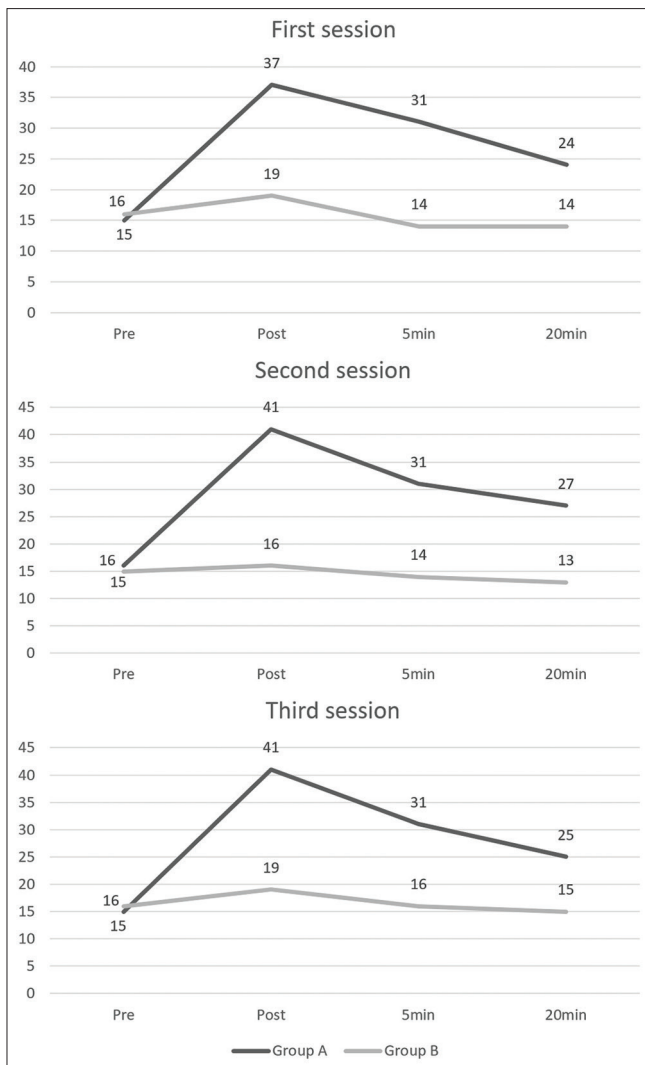
Figure 1: Mean intraocular pressure in each group. Pre: Preinjection, Post: Postinjection, 5 min: 5 minutes after injection, 20 min: 20 minutes after injection

(*P*: 0.857, 0.718, 0.332, 0.652, and 0.142 for global, temporal superior, nasal superior, temporal inferior, and nasal inferior thicknesses, respectively).

DISCUSSION

The intravitreal injection of anti-VEGFs (most of which require multiple injections) has become the choice of treatment in various retinal diseases. One of the concerns in this regard is acute and sustained IOP increases after the injection of anti-VEGFs. Some authors believe that multiple IOP spikes or sustained elevated IOP could induce glaucomatous damage, and so they have proposed several interventions to prevent IOP spikes after intravitreal injection.[6,7] Among them, AC paracentesis is the most effective way to reduce postinjection IOP spikes. However, there is not enough evidence regarding the efficacy and safety of such methods, nor is there any consistency among studies on this treatment method.[4]

In this study, Group B showed significantly lower values of IOP after IVB when compared to Group A. This finding was evident in all measurements (0 min, 5 min, and 20 min) across all three sessions. Figure 1 depicts the time course of the acute IOP rise after injection. In Group A, IOP increased acutely and then followed a downward slope, but after 20 min, it remained significantly higher than that of the baseline. A similar pattern has been described by other studies.[1] In a study by Soheilian *et al.*, the mean IOP after IVB injection remained significantly higher at 30 min in a group without AC paracentesis). Meanwhile, in a group that received AC paracentesis, IOP decreased at a level that remained statistically significant for up to 3 months.[8] In addition, they showed that mean RNFL thickness changes over 3 months were statistically significant between two groups (-2 vs. $0\,\mu$, $P < 0.001$), and they suggested that AC paracentesis prevents peripapillary RNFL loss.[8] This finding is in contrast to ours, as we found that the peripapillary RNFL thickness profile does not change significantly in all sectors. This may be because their participants were older than ours (66 year vs. 62 year) and had thinner baseline RNFL (although it was measured with a different instrument). These factors would make their patients more sensitive to IOP fluctuations. However, most studies have shown that RNFL does not change significantly after the intravitreal injection of anti-VEGF drugs,[9-15] while other reports showed significant RNFL loss related to multiple intravitreal injections.[8,16] This discrepancy across studies may be due to different baseline characteristics of patients, follow-up times, or the number of injections.

On the other hand, the adverse effects of the increased IOP are not limited to RNFL loss and glaucoma damages. Abdolrahimzadeh *et al.* observed macular ganglion cell layer loss after the intravitreal injection of anti-VEGF agents for nAMD. However, the same was not seen in the study by Zucchiatti *et al.*[14,17] Further, Wen *et al.* observed acute reductions in ONH perfusion parameters after intravitreal injections,[18] and Mitsch *et al.* reported impaired vascular autoregulation and oxygen distribution in patients with DME after intravitreal injection of the anti-VEGF agent.[19] Hence, all of them could affect patients' visual function. The short-term stability of RNFL does not obviate the serious consequences of IOP peaks, especially for most retinal conditions that require multiple injections.

In our study, vision-threatening complications (traumatic cataract, vitreous hemorrhage, retinal detachment, and endophthalmitis,) due to intravitreal injection and AC paracentesis were not seen. It was comparable with prior studies which have demonstrated the safety of AC paracentesis before intravitreal injections without sight-threatening complications.[5,20,21]

A significant strength of our study is related to its design (randomized controlled) and the fact that we measured IOP in each of three sessions, thus increasing the validity of the study. In addition, peripapillary RNFL profiles were analyzed

Table 1: Mean peripapillary retinal nerve fiber layer thickness before (-pre) and 1 month after the third (-post) intravitreal bevacizumab injection

	Group A			Group B		
	Mean thickness*	SD	P**	Mean thickness*	SD	P**
Global-pre	110	19	0.816	115	19	0.773
Global-post	111	18		115	19	
TS-pre	145	24	0.198	141	25	0.446
TS-post	141	24		140	26	
NS-pre	124	27	0.604	121	25	0.842
NS-post	141	24		140	26	
TI-pre	149	37	0.126	155	35	0.692
TI-post	144	33		154	32	
NI-pre	125	37	0.849	137	24	0.295
NI-post	124	24		141	35	

*Micrometre, **Paired sample *t*-test. TS: Temporal superior, NS: Nasal superior, TI: Temporal inferior, NI: Nasal inferior, SD: Standard deviation

sector by sector, which allowed us to detect any changes in RNFL that could be missed by total measurements.

However, the study has some limitations as well due to the small sample size, lack of power analysis, short-term evaluation of IOP, short follow-up time, and the RNFL thickness (particular temporal sector), all of which might be affected by macular edema fluctuations. A larger randomized controlled study with a longer follow-up time is required to assess the efficacy and safety of AC paracentesis under these conditions.

In conclusion, there are no statistically significant changes in the peripapillary RNFL thickness after 3 monthly IVB injections. AC paracentesis seems not needed routinely before IVB injection since the short-term effects of IOP spikes on the peripapillary RNFL are not significant.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Hoguet A, Chen PP, Junk AK, Mruthyunjaya P, Nouri-Mahdavi K, Radhakrishnan S, *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 2019;126:611-22.
2. Wen JC, Cousins SW, Schuman SG, Allingham RR. Dynamic changes of the anterior chamber angle produced by intravitreal anti-vascular growth factor injections. Retina 2016;36:1874-81.
3. Morshedi RG, Ricca AM, Wirostko BM. Ocular hypertension following intravitreal antivascular endothelial growth factor therapy: Review of the literature and possible role of nitric oxide. J Glaucoma 2016;25:291-300.
4. Bracha P, Moore NA, Ciulla TA, WuDunn D, Cantor LB. The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: A review. Surv Ophthalmol 2018;63:281-95.
5. Saxena S, Lai TY, Koizumi H, Farah ME, Ferrara D, Pelayes D, *et al*. Anterior chamber paracentesis during intravitreal injections in observational trials: Effectiveness and safety and effects. Int J Retina Vitreous 2019;5:8.
6. Felfeli T, Hostovsky A, Trussart R, Yan P, Brent MH, Mandelcorn ED. Hypotensive efficacy of topical brimonidine for intraocular pressure spikes following intravitreal injections of antivascular endothelial growth factor agents: A randomised crossover trial. Br J Ophthalmol 2019;103:1388-94.
7. Gregori NZ, Weiss MJ, Goldhardt R, Schiffman JC, Vega E, Mattis CA, *et al*. Ocular decompression with cotton swabs lowers intraocular pressure elevation after intravitreal injection. J Glaucoma 2014;23:508-12.
8. Soheilian M, Karimi S, Montahae T, Nikkhah H, Mosavi SA. 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. Graefes Arch Clin Exp Ophthalmol 2017;255:1705-12.
9. Jo YJ, Kim WJ, Shin IH, Kim JY. Longitudinal changes in retinal nerve fiber layer thickness after intravitreal anti-vascular endothelial growth factor therapy. Korean J Ophthalmol 2016;30:114-20.
10. El-Ashry MF, Lascaratos G, Dhillon B. Evaluation of the effect of intravitreal ranibizumab injections in patients with neovascular age related macular degeneration on retinal nerve fiber layer thickness using optical coherence tomography. Clin Ophthalmol 2015;9:1269-74.
11. Valverde-Megías A, Ruiz-Calvo A, Murciano-Cespedosa A, Hernández-Ruiz S, Martínez-de-la-Casa JM, García-Feijoo J. Long-term effect of intravitreal ranibizumab therapy on retinal nerve fiber layer in eyes with exudative age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2019;257:1459-66.
12. Demirel S, Batioğlu F, Özmert E, Erenler F. The effect of multiple injections of ranibizumab on retinal nerve fiber layer thickness in patients with age-related macular degeneration. Curr Eye Res 2015;40:87-92.
13. Sengul EA, Artunay O, Kumral ET, Yenerel M, Rasier R, Kockar A, *et al*. Retinal nerve fiber layer thickness changes in age-related macular degeneration treated with multiple intravitreal ranibizumab. J Ocul Pharmacol Ther 2016;32:665-70.
14. Zucchiatti I, Cicinelli MV, Parodi MB, Pierro L, Gagliardi M, Accardo A, *et al*. Effect of intravitreal ranibizumab on ganglion cell complex and peripapillary retinal nerve fiber layer in neovascular age-related macular degeneration using spectral domain optical coherence tomography. Retina 2017;37:1314-9.
15. Shin HJ, Shin KC, Chung H, Kim HC. Change of retinal nerve fiber layer thickness in various retinal diseases treated with multiple intravitreal antivascular endothelial growth factor. Invest Ophthalmol Vis Sci 2014;55:2403-11.
16. Martinez-de-la-Casa JM, Ruiz-Calvo A, Saenz-Frances F, Reche-Frutos J, Calvo-Gonzalez C, Donate-Lopez J, *et al*. Retinal nerve fiber layer thickness changes in patients with age-related macular degeneration treated with intravitreal ranibizumab. Invest Ophthalmol Vis Sci 2012;53:6214-8.
17. Abdolrahimzadeh S, Gharbiya M, Formisano M, Bertini F, Cerini A, Pacella E. Anti-vascular endothelial growth factor intravitreal therapy and macular ganglion cell layer thickness in patients with neovascular

age-related macular degeneration. Curr Eye Res 2019;44:1000-5.

18. Wen JC, Chen CL, Rezaei KA, Chao JR, Vemulakonda A, Luttrell I, *et al*. Optic nerve head perfusion before and after intravitreal antivascular growth factor injections using optical coherence tomography-based microangiography. J Glaucoma 2019;28:188-93.

19. Mitsch C, Pemp B, Pollreisz A, Gleiss A, Karst S, Scholda C, *et al*. Short-time effect of intravitreal injections on retinal vascular oxygenation and vessel diameter in patients with diabetic macular oedema or neovascular age-related macular degeneration. Acta Ophthalmol 2020;98:e301-8.

20. Meyer CH, Rodrigues EB, Michels S, Mennel S, Schmidt JC, Helb HM, *et al*. Incidence of damage to the crystalline lens during intravitreal injections. J Ocul Pharmacol Ther 2010;26:491-5.

21. Bach A, Filipowicz A, Gold AS, Latiff A, Murray TG. Paracentesis following intravitreal drug injections in maintaining physiologic ocular perfusion pressure. Int J Ophthalmol 2017;10:1925-7.