Hypotensive Effect of Topical Brimonidine Tartarate on Intra-Ocular Pressure Spikes Following Intravitreal Injection of Ranibizumab

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Objective: To study the effect of topical Brimonidine 0.2% eye drops (Brimonidine Tartarate) prophylaxis on intraocular pressure (IOP) spikes following intravitreal injection of Ranibizumab (Lucentis) 0.5mg/0.05ml.

Methods: This is randomized comparative conducted on one hundred non-glaucomatous eyes of one hundred patients. The candidates who were enrolled in the study were randomly classified into two groups; each of which consisted of 50 eyes, fifty eyes with odd and even file numbers. Those with odd file numbers (group A) have not received topical brimonidine tartarate while those with even file numbers have received pre injection topical brimonidine tartarate twenty minutes before the intravitreal injection (group B).

Results: A significant IOP rise was reported in the injected eyes after 30 minutes, and one day after injection (with a mean of 17.58 ± 3.18 mmHg and17.12±2.11 mmHg at 30 minutes and 1 day respectively). A significant lower IOP measures were found in the Prophylactic group compared to unprophylactic group A after 30 minutes and 1 day post injection (mean IOP of 16.56 ± 2.68 and15.12 ±1.99 at 30 minutes and 1 day respectively) (p value less than 0.05).

Conclusion: Topical brimonidine prophylaxis can effectively reduce intraocular pressure (IOP) spikes following intravitreal injection of Ranibizumab (Lucentis) 0.5mg/0.05ml.

Keywords: Brimonidine, Intra-Ocular Pressure Spikes, Intravitreal Injection, Ranibizumab

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Introduction

It has been reported that an increase in IOP from baseline at 60 minutes following intravitreal injection of Anti VEGF is common, with some reported cases experiencing an IOP rise higher than 40 mm Hg[1]. Immediate post injection measures of IOP post-injection in some studies has shown a higher IOP elevations up to 58–87 mm Hg[2].

The mechanism of IOP spikes is still unclear but may be attributed to the expansion of intraocular fluid volume, as well as other factors such as change in ocular size and the facility of ocular flow. Other factors may play a role in IOP spikes such as pre-existing history of glaucoma [3]. This sudden rise of IOP, even if temporary, may lead to a marked decrease in retinal and optic nerve head perfusion[4].

The sustained elevation of IOP is also reported but less common. It may be due to repeated intravitreal injections with repeated IOP spikes and cumulative damage to trabecular meshwork from expansile stress. A threefold increased risk of sustained elevated IOP with an average of 15 intravitreal anti-VEGF injections over 3 years in eyes with no previous open-angle glaucoma has been reported [5].

It's of great importance to monitor IOP after intravitreal injection to provide early management of any IOP rise. Prophylactic measures such as ocular massage with a cotton swab, Honan balloon and pre-injection anterior chamber paracentesis (which is controversial) for the reduction of the immediate IOP spikes following intravitreal injections can be used [6].

Anterior chamber paracentesis carries additional risks, not only more pain and more operative time but also traumatic injuries of the iris, hyphema, inflammation, or even leakage with hypotony or the worst of them endophthalmitis[7].

Several methods have been carried out reduce the risk of IOP as pre-administration of hypotensive eye drops such as brimonidine tartarate. This is an alpha 2-adrenergic agonists that lowers IOP through decreasing aqueous production and increasing uveoscleral outflow and also has a neuroprotective effect making it a good choice for prophylax is from IOP spikes [8,9].

Aim of this work is to study the effect of topical brimonidine eye drops (Jamjoom Pharma, KSA) prophylaxis on intraocular pressure (IOP) spikes following intravitreal injection of Ranibizumab (Lucentis, Genentech, Inc., USA) 0.5mg/0.05ml.

Patients & Methods

This is a prospective study conducted on one hundred non glaucomatous eyes of one hundred patients. All the patients enrolled in the study underwent full ophthalmic examination including visual acuity and intra-ocular pressure (IOP) measurement dilated fundus examination and assessment of the angle of the anterior chamber with 4 mirror goniolens. patients with preoperative narrow angle were excluded from the study

A written informed consent was obtained from each patient included in the study. Ethics committee at faculty of medicine, Alexandria University has approved this study

The candidates enrolled in the study were randomly classified into two groups, each of fifty eyes. The randomization was done according to whether the numbers in the record is even or odd.

Those with odd file numbers have not received topical brimonidine before the intravitreal injection(Group A) while those with even numbers have received topical Brimonidine eye drops (0.2% Brimonidine Tartarate) twenty minutes before injection .(Group B)

Intra-ocular Pressure IOP measured with a Goldman tonometer to both eyes of all patients, one day and thirty minutes before the intravitreal injection then thirty minutes, one day, one week and one month after the intravitreal injection.

Inclusion Criteria: Injection for phakic patients with macular edema due to diabetic retinopathy (DR), central or branch retinal vein occlusion (CRVO or BRVO) and patients with active choroidal neovascularization (CNV).

Exclusion Criteria: A history of previous intravitreal triamcinolone injection, patients with previous history of glaucoma or ocular hypertension, neovascular glaucoma and rubeos isiridis, high IOP prior to injection, patients who were on topical IOP lowering medications. As well as patients with narrow angle on gonioscopy. Patients with aphakia or previous IOL implantation were also excluded .patients with high axial myopia and were excluded (Axial length above 24 or below 21 mm) .Hypersensitivity to Brimonidine drops, pregnancy and lactation were considered also exclusion criteria.

The procedure of intravitreal injection was done under topical anaesthesia. A 10 % povidone-iodine solution was used for sterilization and wash of the conjunctival sac was done with 5 % povidone-iodine solution. Injection of 0.5mg/0.05ml of Ranibizumab at a point located 4mm posterior to the limbus, through the infero-temporal or supero-temporal quadrant with a 27G needle perpendicular, aiming towards the center of the globe.

After injection, a cotton tip soaked with betadine used to press on the injection site to prevent vitreous reflux from the injected site then a drop of topical antibiotic eye drop was installed.

Immediate post-injection test for visual acuity was done in all cases. Cases of IOP rise to the degree affecting central retinal artery (vision drop to hand motion or less confirmed by indirect ophthalmoscopy) had immediate paracentesis and were excluded from the study.

Intra-ocular Pressure was measured with a Goldman tonometer to both eyes of all patients, thirty minutes, one day, one week and one month after the intravitreal injection.

Statistical analysis:

The collected data were reported, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

Results

The preoperative demographic data were analyzed as seen in table 1. there was no statistically significant difference between group B with preoperative prophylaxis with brimonidine eye drops and the group A with no prophylaxis regarding age and sex nor preoperative medical condition.

There was no significant difference found between the two studied groups regarding the indication of Injection: 36%of group (A) and 40% of group (B) had AMD with active CNV. Diabetic macular edema (DME) represented (28%) of group A and (34%) of group While macular edema due to Branch retinal vein occlusion (BRVO) represented 20% and 14% of group A and B respectively. Central retinal vein occlusion (CRVO) cases represented 16% of group A and 12% of group B (Table2).

Although both groups had almost similar baseline IOP in both injected and fellow eyes. A significant IOP rise was reported only in the injected eyes after 30 minutes, and one day after injection, with a significant lower IOP measures Prophylactic group compared to group unprophylactic group only after 30 minutes and 1 day post injection (Table 3).

Table (1): Demographic distribution of the studied groups

Variable	Group A (Unprophylactic group) (n=50)	Group B (Prophylactic group) (n=50)	T	p
Age (yes) Mean ± SD	49.87 ± 3.27	48.65 ± 3.94	1.68	.095
DM	19 (38%)	21 (42%)	.167	.683
HTN	31 (62%)	30 (60%)	.042	.838
Sex				
Female	21 (42%)	23 (46%)	.162	.687
Male	29 (58%)	27 (54%)		

Table (2): Indication of injection in both studied groups

	Group A (Unprophylactic group) (n=50)	Group B (Prophylactic group) (n=50)	T	p
Age-related macular degeneration (AMD) with active CNV	18 (36%)	20 (40%)	1.21	.750
Diabetic macular edema (DME)	14 (28%)	17 (34%)		
Branch retinal vein occlusion (BRVO)	10 (20%)	7 (14%)		
Central retinal vein occlusion (CRVO)	8 (16%)	6 (12%)		

Table (3): Post-injection intra-ocular pressure measures between the two studied groups.

IOP		Group A (Unprophylactic group) (n=50)	Group B (Prophylactic group) (n=50)	T	p
I day pre	Injected eye	14.6 ± 1.87	14.78 ± 1.92	.474	.636
Mean ± SD	Fellow eye	13.6 ± 1.87	13.78 ± 1.92	.474	.600
30 min pre	Injected eye	14.81± 3.87	15.09± 3.62	1.116	.513
Mean ± SD	Fellow eye	13.95 ±2.89	14.17 ±1.56	1.091	.425
30 min post	Injected eye	17.58 ± 3.18	16.56 ± 2.68	2.74	.038
Mean ± SD	Fellow eye	13.28 ± 1.87	13.56 ± 1.94	4.92	.701
1 day post	Injected eye	17.12±2.11	15.12 ±1.99	3.01	.007
Mean ± SD	Fellow eye	13.04 ± 1.50	14.14± 2.14	3.29	.802
1 week post	Injected eye	15.06 ± 1.62	14.76 ± 2.15	.787	.817
Mean ± SD	Fellow eye	13.06 ± 1.99	13.98± 2.22	.723	.850
1 month post	Injected eye	14.98 ± 1.76	14.64 ± 1.64	1.027	.784
Mean ± SD	Fellow eye	13.86± 1.81	13.64 ± 1.59	1.110	.772

Discussion

Intra-vitreal injection therapy is one of the most commonly performed procedures in ophthalmology. Taking into consideration that most patients who need this procedures are old, it is of paramount importance to track any effect on IOP to avoid irreversible damage to the optic nerve . Intra-vitreal injection therapy may cause transient increase in the volume of the eye, which also may lead to transient increase of the intra-ocular pressure (IOP), considering that sustained IOP elevation may increase the risk of developing glaucoma [5].

The volume of the intravitreal injection can directly increase the intraocular pressure (IOP) and there by negatively affect the retinal and optic nerve blood supply [10].

In our study A significant IOP rise was reported only in the injected eyes after 30 minutes, and one day after injection (with a mean of 17.58 ± 3.18 mmHg and17.12±2.11 mmHg at 30 minutes and 1 day respectively), with a significant lower IOP measures in the Prophylactic group compared to

unprophylactic group only after 30 minutes and 1 day post injection(mean IOP of 16.56 ± 2.68 and15.12 ±1.99 at 30 minutes and 1 day respectively) (p value less than 0.05). Our observation of post injection IOP rise was supported by study of **Lee et al. [11],** in which 16 eyes (24.6 %) with diabetic macular edema, 10 eyes (15.4 %) with proliferative diabetic retinopathy, 15 eyes (23.1 %)with exudative age-related macular degeneration, 14 eyes (21.5 %) with retinal vein occlusion-related macular edema, 8 eyes (12.3 %) with chronic central serous chorioretinopathy, and 2 eyes (3.1%) with idiopathic choroidal neovascularization with reporting a significant IOP rise at early post injection follow up.

Similar finding were reported in the work of **Saif et al. [8]**, also in their study, the main indication for injection was diabetic retinopathy 50%.and a significant IOP spike was noticed following injection

Our results were also supported by the work of **Felfeli et al. [9],** as they revealed that topical brimonidine tartrate administered prior to intravitreal injection of anti-VEGF significantly decreases the transient post-injection IOP spike in non-glaucomatous eyes. Our report of IOP was after 30 minutes of injection and this may explain the relatively lower IOP at our report The post-injection IOP was on average 42 mm Hg and reached as high as 81 mm Hg immediately after IVI in unprophylactic patients. Comparatively, the IOP spikes may reach to an average of 34 mm Hg with a high of 63 mm Hg in patients prophylacted with topical brimonidine tartrate which significantly decrease IOP spikes. In addition, they reported that topical brimonidine significantly reduced the likelihood of eyes having an IOP elevation of greater than 20 mm Hg from pre-injection and reaching an IOP greater than 50 mm Hg immediately after injection. In fact, we excluded cases with very high IOP spikes from the study and anterior chamber paracentesis was done to reduce the risk of vision loss.

In the previous study, anterior chamber paracentesis was required for two eyes without prophylaxis that reached an IOP of 70 mm Hg or greater immediately after injection in order to return the IOP to a safe level. The use of anterior chamber paracentesis remains controversial, however, as it does not fully eliminate the potential for ocular damage from a brief sudden IOP rise

Another previous study held by **Kim et al. [13],** evaluating immediate post-injection IOP has suggested that IOP immediately after intravitreal injection may reach as high as 87 mm Hg, but returns to 30 mm Hg at 30 min post-injection.

Brimonidine tartrate is a highly selective alpha2-adrenergic agonist which decrease aqueous production and promote uveoscleral outflow with a good safety profile and its neuroprotective effect leading to significantly visual field progression reduction, so it's easy to incorporate it into practice with the administration of brimonidine tartrate only 20 min prior to intravitreal injection which is effective in reducing IOP spikes **[14].**

Katayama et al. [14], previously demonstrated the effective use of brimonidine administered 90 minutes prior to injection, while administration of brimonidine-timolol only 5 min prior to injection was not shown to have a significant effect on the IOP spike in a study by **Carnota-Méndez et al. [15].**

Some authors have recommended glaucomatous patients to use IOP lowering medication before intravitreal injection of anti-VEGF, while others have recommended monitoring IOP in all patients and treating accordingly. The fact that the risk of sustained IOP increases by threefold with an average of 15 intravitreal anti-VEGF injections over 3 years in eyes with no pre-existing glaucoma may suggest that recurrent IOP spikes may lead to complications even in non-glaucomatous eyes.

In consideration of these findings, patients either non glaucomatous or glaucomatous, their routine use of topical brimonidine tartarate would reduce post intravitreal inection IOP spikes **[16].**

A previous report by **Rasier et al.[18]** revealed an increase not only of IOP but also blood pressure, which was checked 1 week, 3 weeks and 6 weeks after intravitreal Lucentis injection. This variable has not been assessed in our study

According to **Saif et al. [8]** it was found that there was a significant difference, but still within the normal range value in IOP measured 24 h after There was no significant difference between the IOP from one week up to eight weeks of ranibizumab injection.

In the study of **Frenkel et al.[19]** , all 3 intravitreal injections lead to significant initial IOP spikes. The IOP dropped to less than 30mm Hg in all groups within 20 minutes. Prophylactic medication did not prevent post-injection IOP spikes. Patients with and without glaucoma showed a similar rate of IOP normalization over time in all 3 groups.

The effect of topical brimonidine tartrate-timolol given twice a day prior to injection was investigated in a study by **Theoulakis et al. [20]** and was shown to effectively reduce the number of eyes reaching an IOP above 20mm Hg at 15 min post-injection. Other topical agents including apraclonidine, acetazolamide, dorzolamid-timolol

combination and timolol 0.1% gel have also demonstrated efficacy in reducing the mean post-injection IOP when administered 2 hours prior to injections.

Our study has some limitations. Small sample size and lack of long-term outcome for the irreversible effect of IOP on visual filed and optic nerve head. In addition, patient tolerance to topical brimonidine eye drops was not assessed .systemic side effect of both the intravitreal injection of Lucentsi and possible systemic side effect of brimonidine eye drops were not assessed

Conclusion

Topical brimonidine tartrate prophylax is effectively reduces intraocular pressure (IOP) spikes following intravitreal injection of Ranibizumab (Lucentis) 0.5mg/0.05ml.This method of prophylaxis can be readily adopted into current practice of intravitreal injections of anti-VEGF agents.

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References

1. Pang CE, Mrejen S, Hoang QV, et al. ASSOCIATION between needle size, postinjection reflux, and intraocular pressure spikes after intravitreal injections. Retina 2015; 35:1401–6.
2. Zarbin M, Szirth B. Current treatment of age-related macular degeneration. Optom Vis Sci 2007; 84:559–72.
3. Bakri SJ, Ekdawi NS. Intravitreal silicone oil droplets after intravitreal drug injections. Retina 2008; 28(7): 996-1001.
4. Atchison EA, Wood KM, Mattox CG, Barry CN, Lum F, MacCumber MW. The real-world effect of intravitreous anti–vascular endothelial growth factor drugs on intraocular pressure: an analysis using the IRIS registry. Ophthalmology. 2018; 125(5):676-82.
5. Bressler SB, Almukhtar T, Bhorade A, Bressler NM, Glassman AR, Huang SS, Jampol LM, Kim JE, Melia M, Diabetic Retinopathy Clinical Research Network Investigators. Repeated intravitreal ranibizumab injections for diabetic macular edema and the risk of sustained elevation of intraocular pressure or the need for ocular hypotensive treatment. JAMA Ophthalmology. 2015; 133(5):589-97.
6. Pece A, Allegrini D, Montesano G, et al. Effect of prophylactic timolol 0.1% gel onintraocular pressure after an intravitreal injection of ranibizumab: a randomized study. Clin Ophthalmol 2016; 10:1131–8.
7. Helbig H, Noske W, Kleineidam M, Kellner U, Foerster MH. Bacterial endophthalmitis after anterior chamber paracentesis. Br J Ophthalmol.1995; 79:866.
8. Saif, M. Y. S., Abd El Hafez, K. A. E., &Fouad, A. M. Changes in intraocular pressure after intravitreal injection of ranibizumab. NILES Journal for Geriatric and Gerontology. 2020; 3: 23-28.
9. FelfeliT, 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. British Journal of Ophthalmology. 2019; 103(10):1388-94.
10. Bakri SJ, Pulido JS, McCannel CA, Hodge DO, Diehl N, HillemeierJ.Immediate intraocular pressure changes following intravitreal injections of triamcinolone, pegaptanib, and bevacizumab. Eye (Lond). 2007; 23:181–5.
11. Lee CS, Koh HJ. Multiple retinal hemorrhages in diabetic retinopathy after adjunctive intravitreal bevacizumab (Avastin) with pars plana vitrectomy. Acta Ophthalmol Scand. 2007; 85:6-20.
12. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term Intraocular Pressure Changes Immediately After Intravitreal Injections of Anti–Vascular Endothelial Growth Factor Agents. Am J Ophthalmol. 2008; 146:930–4.
13. Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age related macular degeneration. Ophthalmology. 2006; 113:623–32.
14. Katayama BY, Bonini-Filho MA, Messias AM, et al. Comparison of acetazolamide, brimonidine, and anterior chamber paracentesis for ocular hypertension control after initial intravitreal bevacizumab injection: a randomized clinical trial. J Glaucoma 2014; 23: 461–3.
15. Carnota-Méndez P, Méndez-Vázquez C, Otero-Villar J, et al. Effect of prophylactic medication and influence of vitreous reflux in pressure rise after intravitreal injectionsof anti-VEGF drugs. Eur J Ophthalmol 2014; 24:771–7.

16. Bracha P, Moore NA, Ciulla TA, et al. The acute and chronic effects of intravitreal antivascular endothelial growth factor injections on intraocular pressure: A review. SurvOphthalmol2018; 63: 281–95.

17. Rasier R, Artunay O, Yuzbasioglu E, Sengul A, Bahcecioglu H. The effect of intravitreal bevacizumab (avastin) administration on systemic hypertension .Eye (Lond). 2009; 23:1714–8.

18. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006; 355:1432–44.

19. Frenkel MP, Haji SA, Frenkel RE. Effect of prophylactic intraocular pressure–lowering medication on intraocular pressure spikes after Intravitreal injections. Archives of Ophthalmology. 2010; 128(12):1523-7.

20. Theoulakis PE, Lepidas J, Petropoulos IK, et al. Effect of brimonidine/timolol fixed combination on preventing the short-term intraocular pressure increase after intravitreal injection of ranibizumab. Klin Monbl Augenheilkd. 2010; 227:280–4.