Original Article

Comparison of Intravitreal vs Intracameral Bevacizumab effectiveness

A Prospective Study Analyzing Short Term Effects of Intravitreal versus Intracameral Bevacizumab on Neovascular Glaucoma

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ABSTRACT

Objective: A single centre prospective trial to study the short term efficacy of Intracameral versus intravitreal Bevacizumab 2.5mg in 0.1mlfor the treatment of neovascular glaucoma in terms of iris neovessel regression and control of intraocular pressure.

Study Design: Comparative / Interventional Study

Place and Duration of Study: This study was conducted at the Bodla Eye Care, Multan from March 2015 till April 2016.

Materials and Methods: A total of 24 patients were recruited in the study. Study end point was 28 days/one month post intervention. Primary etiology of neovascular glaucoma was proliferative diabetic retinopathy and central retinal vein occlusion. Patients were divided into group A for intravitreal and Group B for Intracameral injections. Both groups received 2.5 mg in 0.1 ml of Bevacizumab administered by single surgeon in same settings.

Results: There was no significant change in pre and post-operative visual acuity in both groups. There was a remarkable regression of iris neovessel in both groups. Reduction in IOP was clinically significant in both groups i.e. $p<0.01$ for group A and $p<0.05$ for group B. Intracameral group was found to have more remarkable regression of fibro vascular membranes.

Conclusion: Intracameral injections of bevacizumab appears to be as effective as intravitreal administration of the drug for the short term control of pathology. Intracameral injections especially in Pseudophakics carries relative fewer incidences of devastating complications as endophthalmitis. Moreover IOP spikes post Intracameral injections are fewer after performing an anterior chamber paracentesis at the same time.

Key Words: Intravitreal, Intracameral Bevacizumab, Neovascular Glaucoma

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INTRODUCTION

Neovascular glaucoma is a type of secondary glaucoma which is most refractory to treatment.[1,2] Pathology appears to be formation of a fibro vascular membrane over the anterior surface of iris and angles, clogging trabecular meshwork.[1,3] Neovascularization of the iris NVI is the hallmark of the disease, hence the name rubeotic glaucoma.[4] Neovessel formation is a direct result of hypoxia with retinal vein occlusion and diabetic retinopathy as the commonest cause.[3,5] Ischemia leads to raised level of vascular endothelial growth factor VEG-F and subsequent neovascularization. These vessels are associated with fibrous tissue formation which leads to fibro vascular membranes in the anterior chamber.[6] Lee et al reported an incidence of NVI as high as 2.5% in patients presenting with proliferative diabetic retinopathy.[7,17]

It is expected that we are going to see soaring numbers of mentioned pathology especially in our society as diabetes has taken the form of a pandemic. Author strongly believes it is extremely important to have published local demographic data especially from rural South Punjab, so that we can better understand the severity of the disease.

Bevacizumab (Avastin) has undoubtedly become one of the commonest therapeutic agent in ophthalmology over the last decade.[9] It is a humanized, full length antibody to counter the effects of vascular endothelial growth factor. Several studies have been published for its use in diabetic macular oedema and wet age related macular degeneration (Rodrigo et al. 2006; Ryan et al. 2006). There have been studies for its use in neovascular glaucoma.[12,13] Bevacizumab is associated with remarkable regression of iris neovessel. The effect of single injection has been reported to last for as long as three months.[6,13] Hence it is possible to have an optimum control of intraocular pressure for the mentioned time period.

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Ungreanu et al has published a similar study looking at the effect of Bevacizumab in neovascular glaucoma.[9] They however had used separate doses for Intracameral and intravitreal injections. Since in our region we primarily have access to prefilled bevacizumab syringes with dose titration not possible, authors considered it very important to conduct this prospective trial using standard bevacizumab formulation i.e. 2.5mg in 0.1 ml.

It is frequently observed that in the long term Bevacizumab alone is not sufficient for intraocular pressure.[14] Treatment needs to be complemented with pan retinal photocoagulation, cyclodiode laser and glaucoma valve surgery. Nevertheless Anti-VEGF is of critical importance in acute management of the pathology.

MATERIALS AND METHODS

This was an Comparative / Interventional Study with patients recruited from two sites, Multan Medical and Dental College, Multan and Bodla Eye Care, Multan. Study was carried out at Bodla Eye Care due to availability of resources and ease of logistics. Both are privately owned tertiary eye care facilities. Patients were recruited over a period of one year and were assigned a study identification number starting from 1 to 24 according to their time of induction in the study. All odd number 1,3,5… were assigned to group A and all even numbers 2,4,6…to Group B. An informed consent was obtained from the patients. They were informed in details about the procedure and possible risks involved. Inclusion criteria were rubeosis iridis with raised intraocular pressure. Exclusion criteria were previous history of primary open angle glaucoma, Anti-VEGF injections, glaucoma surgery or intravitreal corticosteroids injections.

Twelve patients were assigned each to group A and group B. In Group A 9 patients had proliferative diabetic retinopathy, two central retinal vein occlusion while one had branch retinal vein occlusion as the cause for rubeotic glaucoma. Out of twelve patients in Group B, ten had proliferative diabetic retinopathy while two had central retinal vein occlusion.

Patients had a thorough slit lamp assessment. Intraocular pressure measurements were taken using Goldman tonometer. All patients underwent detailed gonioscopic assessment to confirm the presence of fibrovasular membranes.

Group A patients had IOP ranging from 29-55mmof Hg with mean IOP of 41mm of Hg. Group B had IOP ranging from 31-58mmf Hg with mean IOP of 40 mm of Hg. Group A patients had a standard dose of Bevacizumab 2.5 mg in 0.1 ml. Injections were obtained in prefilled syringes from the same distributor. Procedure was performed by single surgeon in operation theatre under sterile conditions. Preoperatively all patients had oral acetazolamide 500 mg to reduce the risk of central retinal artery occlusion secondary to volume expansion with raised intraocular pressure.5% Povidone Iodine was used to achieve sterile periocular area. A drop of Povidone Iodine along with Alcaine (Alcon) was instilled in conjunctival sac. Bevacizumab was injected from prefilled syringes with 30 gauge needle. Site of injection was 3.0mm in pseudophakic and 3.5mm in phakic patients. Infero temporal quadrant was used in all patients as site for injection. Patients were prescribed with topical ofloxacin eye drops to be used four times a day for five days. They were advised to continue with their intraocular pressure lowering medication for a period of two weeks post injection. Patients were seen on day 1, day 14 and day 28 post injection, i.e. study end point.

In Group B, all patients had the standard 2.5mg Bevacizumab in prefilled syringes obtained from the same source. All procedures were performed by single surgeon. Patients had oral Acetazolamide 500mg prior to the procedure. Procedure was performed in operating room under sterile conditions. Povidone iodine was used to clean periocular surface and conjunctival sac. An anterior chamber tap was performed to replace equivalent volume i.e. 0.1ml of aqueous with Bevacizumab. This is to ascertain that patient would not end up with high intraocular pressure spike. Patients were advised to continue with IOP lowering treatment that they are already on for next two weeks. They were prescribed with topical ofloxacin to be used four times a day for five days. Patients were followed up on day one, day 14 and day 28 of the procedure.

Post operatively patients had a detailed ophthalmic assessment, including slit lamp examination and gonioscopy. Amount of residual rubeosis was determined and assessed with detailed iris assessment. Gonioscopy was performed to evaluate for the amount of persistent fibro vascular membranes. Intraocular pressure was measured using Goldman tonometer.

RESULTS

Bevacizumab was found to be an effective treatment modality for the short term treatment of neovascular glaucoma. No serious side effects were noted in either group with significant reduction of intraocular pressure. Patient's ages ranged from 32 to 91 years with mean age of 59 years. Out of total participants 18 (75%0 were male while 6 (25%) were females. Primary etiology of neovascular glaucoma was found to be in 14 (58%) patients. 6 patients had central retinal vein occlusion i.e. 24% and the rest i.e. 16% had branch retinal vein occlusion as the cause for rubeotic glaucoma. Visual acuity was measured using log MAR charts Mean visual acuity changed from 1.4 preoperatively to 1.1 post operatively though change was found to be non-significant.

Day 1 Assessment: All operated patients were assessed on day 1 of the study. Slit lamp examination was performed to assess for any intraocular inflammation. IOP measurements were taken with Goldman tonometer. No serious side effects as endophthalmitis or vitreous haemorrhage was identified. One patient from GroupA had a corneal abrasion which subsequently healed in 48 hours.

Week 2 Assessment: Patients from Group A and B were analyzed at the end of week 2 i.e. 14 days post procedure. They had a slit lamp examination, IOP

measurement as well as gonioscopic assessment. In Group A patients there was significant resolution of fibro vascular membrane in all apart from one who presumably developed an anterior chamber hyphemain the week one. Patients had a mean IOP of 33 mm. Group B patients had very similar results in term of fibro vascular membrane regression and IOP reduction. Group B patients had a mean IOP of 28 mm of Hg. It was noticed that fibro vascular membrane resolution was more significant in Group B than A, though this is author's subjective assessment.

Week 4 Assessment: Week 4 i.e. day 28 was considered as endpoint for this study. All patients had slit lamp assessment, gonioscopic assessment as well as Goldman tonometry. . There was remarkable regression of fibrovasular membranes in all patients of both groups. Mean intraocular pressure in Group A had reduced to 26mm of Hg while it was 24mm of Hg in Group B.Reduction in IOP was clinically significant in both groups i.e. $p<0.01$ for group A and $p<0.05$ for group B. Fibrovasular membranes were almost nonexistent on gonioscopic assessment with more remarkable results in Group B.

DISCUSSION

Neovacular glaucoma always poses a challenge to clinicians in terms of effective management.[15] In an acute stage it is refractory to topical as well as systemic treatment with limited surgical options. Bevacizumab over a period of last few years has proven to be an efficient drug in acute management of neovascular glaucoma.[1,17] A single injection of bevacizumab either administered through intravitreal approach or in anterior segment provides effective control of intraocular pressure with regression of fibro vascular membranes.[18] One limitation is its short duration of action. It's effect tends to wear off in 30 to 90 days. However it has been observed that in many occasions a single injection of Bevacizumab is effective for the management of neovascular glaucoma during this time period. It also provides ample time and opportunity for other management e.g. panretinal photocoagulation, cyclodiode therapy e.t.c. to takes there effect.

There is always a debate on ideal site of administration, dosage and complications. [11,14,16] Authors have tried to address these issues in this study keeping in view the resources available in an under developed country as Pakistan. The culprit in rubeotic glaucoma is vascular endothelial growth factor produced as a result of retinal ischemia but etiology lies in rubeosis formation in anterior segment. This justifies the administration of drug from both sites.

In our study we have tried to determine the preffered site for injection, optimum dosage and its effects in the short term. It was not the scope of this study to monitor long term effects or explore other surgical options, hence the endpoint of study was four weeks starting from the day of intervention. In this study we used the standard dosage of Bevacizumab 2.5 mg/0.1ml for intracameral and intravitreal administration. Authors consider this as the most vital question to be answered as other studies have used a reduced dose of Bevacizumab.[19] In Pakistan majority of facilities use Bevacizumab in prefilled sringes with standard dosage, hence it is important to determine the safety and efficacy of standard Bevacizumab concentration for local population. In our study proliferative diabetic retinopathy was the causative etiology in 58% of the patient. Contrary to this

In our study there was no significant improvement in visual acuity post procedure. This is contrary to what has been reported in some studies e.g. Hayreh et al. In the west retinal vein occlusion has been the main cause for neovascular glaucoma.[20,21] This shows the severity of diabetes and its related complications due to lack of screening facilities that prevails in third world in general and Pakistan in particular.

In a study done by Asaad A Gahnem et al, there was a 60% improvement in BCVA followed by bevacizumab. In our study mean visual acuity improved from 1.4 LogMAR to 1.1 LogMAR, this difference how ever was not found to be statistically significant.[17,21] A possible explanation can be late presentation and chronicity of disease. Moreover mean visual acuity in our study was less than what has been noticed by Asaad A Gahnem, this again confirms the hypothesis regarding late presentation as mentioned earlier.

In another study by Khettab et al, mean visual acuity kept on improving over a period of three months post Bevacizumab. Authors do agree with this observation but obviously our study was limited to four weeks hence it is not possible to make a direct comparison.[17,21]

There was a remarkable regression of NVI's in all patients post bevacizumab in our study. This finding has been confirmed by several studies done in the past. Gahnem et al reported a 100% regression of NVI's on second post op day post Bevacizumab. There has been a reported recurrence of NVI's with an incidence of as high as 50%. Again it is not possible to have a direct comparison for this finding.

Chalam et al reported an interesting finding in their study of nine patients of which eight did not required glaucoma surgery following bevacizumab. Authors do agree with these findings as all of our patients had a decrease in IOP as well as regression of fibro vascular membranes at least in the follow up period.[16,21]

In our study Intracameral injection led to a fast and more remarkable regression of neovascular membranes. These findings are consistent with Purvi et al who also found intracameral Bevacizumab, superior to intravitreal in terms of disease control.[8] Moreover it carries lesser incidence of devastating compilations as endophthalmitis. Anterior chamber hyphema has been reported as a possible complication of Intracameral injections. We, in our study did have a patient with anterior chamber hyphema but this is a self-limiting complication and in no way can be compared to endophthalmitis.

There has been reported occurrence of decompression retinopathy. Authors did not come across this

complication in either of their cases. This can be avoided with careful paracentesis as was meticulously performed for all of our patients in Group B.

CONCLUSION

In conclusion, our study determines that the Intracameral Bevacizumab in the standard 2.5mg/0.1ml dose is effective and reliable for treating rubeotic glaucoma. It carries a lesser incidence of complications with enhanced regression of angle rubeosis and fibro vascular membranes. We did not encountered anterior segment toxicity in any of our patients. This study has major limitations in term of sample size and duration of follow up. Authors believe there is a need for similar study with larger sample size and longer follow up to revalidate our results.

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Moraczewski AL, Lee RK, Palmberg PF, et al. Outcomes of treatment of neovascular glaucoma with intravitreal bevacizumab. Br J Ophthalmol 2009;93:589–593.
2. Wakabayashi T, Oshima Y, Sakaguchi H, et al. Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal disease in 41 consecutive cases. Ophthalmol 2008;115(9): 1571–1580.
3. Duch S, Buchacra O, Milla E, Andreu D, Tellez J. Intracameral bevacizumab (Avastin) for neovascular glaucoma: a pilot study in 6 patients. J Glaucoma 2009;18(2):140–143.
4. Davidorf FH, Mouser JG, Derick RJ. Rapid improvement of rubeosis iridis from a single bevacizumab (Avastin) injection. Retina 2006; 26:354–356.
5. Yuzbasioglu E, Artunay O, Rasier R, Sengul A, Bahcecioglu H. Simultaneous intravitreal and intracameral injection of bevacizumab (Avastin) in neovascular glaucoma. Ocul Pharmacol Ther 2009; 25(3):259–264.
6. Alkawas AA, Shahien EA, Hussein AM. Simultaneous intravitreal and intracameral injection of bevacizumab (Avastin) in neovascular glaucoma. J Ocul Pharmacol Ther 2009;25(3): 259–264.
7. Toklu Y, Cakmak HB, Raza S, Anayol A, Asik E, Simşek S. Short-term effects of intravitreal bevacizumab (Avastin(®)) on retrobulbar hemodynamics in patients with neovascular age-related macular degeneration. Acta Ophthalmol 2011;89:41–45.
8. Bhagat PR, Agrawal KU, Tandel D. Study of the Effect of Injection Bevacizumab through Various Routes in Neovascular Glaucoma. J Curr Glaucoma Pract 2016;10(2):39–48.
9. Ungureanu E, Geamanu A, Popescu V, Dinu I, Grecescu M, Gradinaru S. Comparison between the efficacy and side effects of intravitreal versus anterior chamber Bevacizumab injection in neovascular glaucoma patients. J Med Life 2014; 7 (Spec Iss 4): 68–70.
10. Parodi M, Iacono P. Photodynamic therapy for neovascular glaucoma. Ophthalmol 2005;112: 1844–1845.
11. Avery R. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin®) treatment. Retina 2006;26:351–354.
12. Davidorf F, Mouser G, Derick R. Rapid improvement of rubeosis iridis from a single bevacizumab (Avastin®) injection. Retina 2006; 26:354–356.
13. Paula S, Jorge R, Costa A, Rodrigues Mde L, Scott IU. Short-term results of intravitreal bevacizumab (Avastin®) on anterior segment neovascularization in neovascular glaucoma. Acta Ophthalmol Scand 2006;84:556–557.
14. Grisanti S, Biester S, Peters S, Tatar O, Ziemssen F. Intracameral bevacizumab for iris rubeosis. Am J Ophthalmol 2006;142:158–160
15. Mason J, Albert M, Mays A, Vail R. Regression of neovascular iris vessels by intravitreal injection of bevacizumab. Retina 2006;26:839–841.
16. Batioğlu B, Astam N, Özmert E. Rapid improvement of retinal and iris neovascularization after a single intravitreal bevacizumab injection in a patient with central retinal vein occlusion and neovascular glaucoma. Int Ophthalmol 2008;28: 59–61.
17. Lee SJ, Lee JJ, Kin SY, Kim SD. Intravitreal bevacizumab (Avastin®) treatment of neovascular glaucoma in ocular ischemic syndrome. Korean J Ophthalmol 2009;23:132–134.
18. Hasanreisoglu M, Weinberger D, Mimouni K, et al. Intravitreal bevacizumab as an adjunct treatment for neovascular glaucoma. Eur J Ophthalmol 2009; 19:607–612.
19. Gupta V, Jha R, Rao A, Kong G, Sihota R. The effect of different doses of intracameral bevacizumab on surgical outcomes of trabeculectomy for neovascular glaucoma. Eur J Ophthalmol 2009;19:435–441.
20. Jaissle G, Szurman P, Bartz-Schmit K. Recommendation for the implementation of intravitreal injections – statement of the German Retina Society, the German Society of Ophthalmology (DOG) and the German Professional Association of Ophthalmologists (BVA) Klin Monatsbl Augenheilkd 2005;225: 390–395.
21. Iliev M, Domig D, Wolf-Schnurrbursch U, Wolf S, Sarra G. Intravitreal bevacizumab (Avastin®) in the treatment of neovascular glaucoma. Am J Ophthalmol 2006;142:1054–1056.