Original Article

Short and long term intraocular pressure changes after intravitreal injections of triamcinolone acetonide and bevacizumab in diabetic macular edema

Mahmood Ali, Furqan Ahmad Khan, Sarah Zafar, Farah Akhtar

Al-Shifa Trust Eye Hospital Rawalpindi

Objective: To compare the short and long term intraocular pressure (IOP) changes after intravitreal injections of triamcinolone acetonide and bevacizumab in diabetic macular edema.

Methodology: The hospital based randomized clinical trial was conducted from Jan 1, 2012 to December 31, 2012 and included 60 patients with diabetic macular edema. 30 were injected with intravitreal triamcinolone acetonide (IVTA) and 30 with intravitreal bevacizumab (IVB). IOP was recorded before injection, at 1week and 6 weeks after injections. Results were analyzed using SPSS v 13.0.

Results: Difference in mean IOP of the two groups was not significant at base line (p=0.765) and 1 week (p=0.560). However, at 6 weeks, mean IOP in IVTA was significantly raised from base line (p<0.001) and was also higher than mean IOP of IVB group at that follow up (p<0.001).

Conclusion: Although effect on IOP was not significant in short term but patients in IVTA group had significantly higher IOP at 6 weeks after injection. This warrents careful patient selection and regular monitoring of IOPs in cases treated with intravitreal injections. (Rawal Med J 2014; 39:443-445).

Key words: Diabetic macular edema, bevacizumab, triamcinolone acetonide, intra ocular pressure, anti VEGF.

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of visual loss in diabetics. Factors like disruption in the blood retinal barrier, hypoxia, altered blood flow, retinal ischemia and vitreomacular interface changes are associated with the pathogenesis and progression. Recent research has established that vascular endothelial growth factor (VEGF) plays an essential role in increasing retinal vascular permeability as a result of blood-retinal barrier breakdown.[1] As a result many anti VEGF drugs are now being used in the management of DME. Bevacizumab (Avastin) is a full-length, recombinant humanized antiVEGF monoclonal antibody that binds to all isoforms of VEGF-A. It is now being used off label in treatment of various retinal diseases utilizing its anti-angiogenic and anti-exudative effects.[2,3] Most frequently used dosage of intravitreal bevacizumab (IVB) is 1.25mg/0.05ml and 2.5mg/0.1ml.[4]

Triamcinolone acetonide (TA) is a glucocortcoid and has anti-inflammatory, angiostatic and VEGF suppressive effects. It is also being widely used in the treatment of DME. The exact mechanism of action of intra vitreal triamcinolone acetonide (IVTA) is unknown, but the rationale behind its usage lies in the ability to inhibit arachnoid pathway, down regulate the production of cytokines, and reduce breakdown of blood retinal barrier.[5] After delivery into vitreous cavity, the drug attaches to the collagen net of the vitreous and persists in the cavity for months.[6] The complications of IVTA include increase in IOP, posterior sub capsular cataract, postoperative infectious endophthalmitis and noninfectious endophthalmitis.[7]

The choice of drug for intravitreal injection is dependent on many factors like severity of edema, deposition of hard exudates at macula, response to previous treatment as well as cardiovascular status of the patient.[8] Apart from clinical effects, financial impact of the treatment can also be an important factor regarding choice of therapy, as multiple sessions may be required.[9,10] The objective of this study was to compare the safety of IVTA and IVB in DME considering short and long term changes in IOP.

METHODOLOGY

This study was carried out at Al-Shifa Trust Eye Hospital Rawalpindi from January 1, 2012 to December 31, 2012 in which 60 patients with DME were included by non-probability convenience sampling. Approval from the hospital Ethical Committee was obtained. All patients underwent a detailed anterior and posterior segment examination including IOP assessment. All had pre operative IOP less than 18 mm of Hg using Goldmann applanation tonometer. Patients with a history of prior intraocular, peribulbar or systemic steroids, cataract surgery with in past one year, uncontrolled diabetes mellitus, uncontrolled hypertension, myocardial infarction, stroke and patients who were not available for a follow-up of at least 6 weeks were excluded from the study. Glycemic status was considered as "good control" if HbA1c was <% and "poor control" if HbA1c ?7%.[11] Patients with poor control were excluded. Any complication during the procedure also lead to exclusion of the subjects from the study.

The patients were divided in to two equal groups. Group A received intravitreal 4.0mg/0.1ml of triamcinolone acetonide and Group B received 1.25mg/0.05 ml of bivacizumab. After the injections, topical ofloxacin eye drops were prescribed for 7 days along with oral tablet ciprofloxacin 500 mg b.d for three days. IOP was measured after one week and 6 weeks.

Data were analyzed using SPSS version 13. Independent sample 't' test was used to compare mean IOPs between the two groups while paired sample t test was applied to compare mean IOPs at different follow ups within same group. A $p<0.05$ was considered as statistically significant.

RESULTS

The mean age of patients in group A was 63.25±4.80 years while for group B it was 65.10±5.20 years ($p=0.232$). Mean base line IOP was 15.12±2.60 mm of Hg in group A (IVTA) and 14.85±2.40 mm of Hg in group B (IVB). Difference in IOP was insignificant at base line ($p=0.765$) and 1st post op week ($p=0.560$). At 6 weeks, mean IOP in IVTA significantly higher from its base line ($p<0.001$) and was also significantly higher than mean IOP of IVB group at that follow up with $p<0.001$ (Table).

Table. Comparison of IOP between IVTA and IVB groups (mm Hg).

Timing	Group A IVTA	Group B IVB	P value
Before injection	15.12 ± 2.60	14.85 ± 2.40	0.765
1 week Post injection	15.88 ± 2.83	15.25 ± 2.63	0.560
6 weeks Post injection	18.35 ± 5.45	14.55 ± 2.85	<0.001

In the IVTA group, 3 (10%) patients developed IOP more than 25 mm of Hg at 6 weeks, which normalized after topical anti glaucoma treatment. In the IVB group, there was no case of IOP increase more than 25 mm of Hg, requiring IOP reduction treatment.

DISCUSSION

The current study showed that there were less chances of IOP rise in short term after IVTA or IVB. However, on long term basis eyes treated with IVTA were at a greater risk of IOP increase. Possible cause of IOP rise after intravitreal injection on short term basis may be mechanical, as a result of increase in vitreous volume. We used different volumes for IVTA (0.1ml) and IVB (0.05 ml), however, both volumes did not produce any significant change in IOP at one week. At 6 weeks, increase in IOP in IVTA group may be explained by corticosteroid-dependent biochemical changes resulting in increased aqueous outflow resistance related to an accumulation of extracellular matrix material in trabecular meshwork.[7,8]

Similar results have been reported in various studies. Significant change from baseline in mean IOP was seen at 4 weeks in IVTA group compared to IVB.[12] Triamcinolone 4 mg raised IOP about 20% from baseline at 3 months post injection.[13] Azad R compared the results of three treatment modalities intravitreal bevacizumab, intravitreal triamcinolone acetonide, and macular grid augmentation in refractory diffuse diabetic macular edema. No case of IOP rise was reported in IVB group while 8 (40%) eyes in IVTA Group had IOP rise and 10 (50%) eyes developed cataract.[14]

IVTA of 20 mg for various pathologies including DME raised IOP readings higher than 21 mmHg in 41.2% patients while 1.8% developed IOP more

than 40 mmHg and occurred in younger age.[15] The current study only included cases of DME with a mean age of around 65 years so association of IOP with age was not studied. Due to the possible risk of IOP rise with IVTA injection, IVB is currently becoming more popular in cases with already high IOPs prior to intervention.[16]

CONCLUSION

Although effect on IOP was not significant in short term, patients in IVTA group had significantly higher IOP at 6 weeks after injection. This warrents careful patient selection before drug administration and regular monitoring of IOPs in DME cases treated with intravitreal injections.

Author contributions:
Conception and design: Furqan Ahmad Khan
Collection and assembly of data: Sarah Zafar, Mahmood Ali
Analysis and interpretation of the data: Mahmood Ali, Furqan Ahmad Khan
Drafting of the article: Mahmood Ali
Critical revision of the article for important intellectual content: Farah Akhtar
Statistical expertise: Farah Akhtar
Final approval and guarantor of the article: Mahmood Ali
Corresponding author email: Dr. Mahmood Ali: drmahmood_shifa@yahoo.com
Conflict of Interest: None declared
Rec. Date: Jun 17, 2014 Accept Date: Sep 15, 2014

REFERENCES

1. Lee K, Chung H, Park Y, Sohn J. Efficacy of Intravitreal Anti-vascular Endothelial Growth Factor or Steroid Injection in Diabetic Macular Edema According to Fluid Turbidity in Optical Coherence Tomography. Korean J Ophthalmol 2014;28:298-305.
2. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:280516.
3. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. Br J Ophthalmol 2006;90:1344-9.
4. Mason JO 3rd, Albert MA Jr, Vail R. Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. Retina 2006;26:356-7.
5. Gillies MC, Sutter FK, Simpson JM, Larsson J, Ali H, Zhu M. Intravitreal triamcinolone for refractory diabetic macular edema: Two-year results of a double masked, placebo-controlled, randomized clinical trial. Ophthalmology 2006;113:1533-8.
6. McCuen BW 2nd, Bessler M, Tano Y, Chandler D, Machemer R. The lack of toxicity of intravitreally administered triamcinolone acetonide. Am J Ophthalmol 1981;91:7858.
7. Conway MD. The problem of pressure elevation associated with intravitreal triamcinolone. Br J Ophthalmol 2006;90:934-5.
8. Jonas JB, Kreissig I, Degenring RF. Intravitreal triamcinolone acetonide for treatment of intraocular proliferative, exudative and angiogenic diseases. Prog Ret Eye Res 2005;5:587611.
9. Stein JD, Newman-Casey PA, Kim DD, Nwanyanwu KH, Johnson MW, Hutton DW. Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema. Ophthalmology 2013;120:1835-42.
10. Pershing S, Enns EA, Matesic B, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of treatment of diabetic macular edema. Ann Intern Med 2014;160:18-29.
11. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. J Diabetes Complications 2010 ;24:84-9.
12. Paccola L, Costa RA, Folgosa MS, Barbosa JC, Scott IU, Jorge R. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). Br J Ophthalmol 2008;92:76-80.
13. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109:9207.
14. Azad R, Sain S, Sharma YR, Mahajan D. Comparison of intravitreal bevacizumab, intravitreal triamcinolone acetonide, and macular grid augmentation in refractory diffuse diabetic macular edema: A prospective, randomized study. Oman J Ophthalmol 2012;5:166-70.
15. Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeter BA. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology 2005 ;112:593-8.
16. Kernt M, Neubauer AS, Kampik A. Intravitreal bevacizumab (Avastin) treatment is safe in terms of intraocular and blood pressure. Acta Ophthalmol Scand 2007;85:119-20.