Original Research Article

Efficacy of Intravitreal Bevacizumab versus Intravitreal Triamcinolone for treatment of Uveitic Macular Edema in tertiary care hospital of Jharkhand

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Abstract

Background: Uveitic macular edema is most common cause of visual impairment in both infectious and non-infectious uveitis. It accounts for more than 30% cases of active uveitis. **Purpose:** To compare the effects of Intravitreal injections of Bevacizumab and Triamcinolone for the treatment of Cystoid macular edema in non-infectious uveitis. **Methods:** 40 eyes of 35 consecutive patients with CME associated with non-infectious uveitis were divided to 2 groups. 20 eyes were treated with 1.25mg of IVB and 20 eyes received 4mg of IVT. The clinical course of Best corrected visual acuity, Intraocular pressure and Central macular thickness by Optical Coherence Tomography was monitored for up to 6 months after the initial injection. **Results:** The best visual acuities were achieved 1 month after injection in both groups. In IVB group improvement in Visual acuitywas achieved in 16/20(80%) of eyes and in IVT group was 19/20(95%). In IVT group intraocular pressure was found to be raised. The Central macular thickness reduction in the IVT group wasfrom 298.52µ to 197.68µ and in IVB group was from 311.76µ to 227.13µ. **Conclusion:** Both IVB and IVT treatments can effectively improve Best corrected visual acuity and reduce Central macular thickness in Uveitic Cystoid macular edema patients. The Central macular thickness reduction was greater in IVT groupthan IVB group. The IVT group causes increase in intraocular pressure.

Keywords: Cystoid macular edema, Intravitreal injections, Triamcinolone Acetonide, Bevacizumab, Central macular thickness

Introduction

Uveitis is inflammation of the uveal tract. On the basis of predominant site of inflammation it can be classified into anterior uveitis, intermediate uveitis, posterior uveitis and pan uveitis[1]. Uveitic macular edema is most commonly associated with non-infectious causes of intermediate uveitis, posterior uveitis and pan uveitis. In anterior uveitis macular edema is uncommon but if present, it is most commonlyseen in HLA B27 patients. UME is the most common cause of diminution of vision in one-third cases of posterior uveitis[2]. In non-infectious uveitis, macular edema is the most common vision threatening complication and seen in one-tenth of the cases[3].

Macular edema is the accumulation of fluid within the retinal layers as cystoid spaces or diffuse retinal thickening or in the sub retinal space between the neurosensory retina and retinal pigment epithelium. The first two mechanisms occur due to breakdown of inner and outer blood- retinal barriers lead to fluid accumulation by increased vascular permeability. This is mediated by pro-inflammatory cytokines such as interleukin-2, interleukin-10, TNF-alpha and VEGF, protein kinase C and prostaglandins[4, 5]. The third mechanism results from the failure of normal physiological process.

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In a normal functioning retina RPE cells act to eliminate fluid from the retina. If this function is compromised fluid may accumulate in the retina.

Macular edema can be assessed clinically by using slit- lamp fundus bio microscopy and fluorescein angiography. Fluorescein angiography is an invasive procedure which requires intravenous dye and stereo photographic imaging testing. In recent times Optical coherence tomography is a non-invasive imaging technique which is more sensitive and it detects not only the presence of macular edema but also measures macular thickness. Hence Ithas become a preferred imaging modality for the evaluation and monitoring of treatment response of macular edema[6, 7].

The treatment of non-infectious Uveitic CME consists of controlling the source of inflammation. Treatment options are non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents and biological agents[7, 8]. The routes of administration are topical, local, Intravitreal and systemic. In Intravitreal route low dose of drug is administered because it achieves higher concentration in the target areas with less systemic absorption compared with other routes of drug delivery. It avoids the risk of side effects associated with severe systemic effects.Ocular side effects arevitreous haemorrhage, cataract, glaucoma, endophthalmitis and retinal detachment but the incidence of such complications are relatively low[9].

Recently there has been tremendous improvement in Intravitreal anti VEGF therapy for many ocular diseases such as CME, choroidal neovascularisation, neovascular glaucoma, coat's disease, retinal neovascularisation, radiation induced-induced retinopathy. Bevacizumab and Ranibizumabare most commonly used Anti- VEGF

Monoclonal antibody used in patients of Uveitic macular edema. According to a study of Acharya et al, Ranibizumab is useful in decreasing macular edema and improving vision in Uveitic patients.

The main outcomes of this study were measured in form of Central Macular Thickness(CMT) and log MAR of Best Corrected Visual Acuity(BCVA). IOP had been also measured and compared in both groups of patients.

Materials and methods

This was a Comparative Prospective study done in tertiary care hospital, Regional institute of Ophthalmology, Rajendra Institute of Medical Sciences, Ranchi, India from January 2021 to June 2021. This study was conducted in accordance with the tenets of the declaration of Helsinki and was approved by departmental research committee.

Allpatients of non-infectious uveitis with macular edema were included in study.Patients with history of infectious uveitis and other ocular diseases like diabetic retinopathy, retinal vascular obstruction with macular edema were excluded from the study.

Written informed consent taken from all the patients after explaining the procedure. All patients underwent a complete ophthalmic examination which includes measures of the best-corrected visual acuity(BCVA), intraocular pressure(IOP), slit-lamp examination and dilated fundus examination. All the patients of non-infectious uveitis who had decreased vision due to cystoid macular edema (CME) and were not responding to topical corticosteroids were tested with Stratus Optical Coherence Tomography (OCT) Carl Zeiss Meditech, Inc, Dublin, California.

40 eyes of 35 consecutive patients with CME associated with non-infectious uveitis were divided into 2 groups. 20 eyes were included in group 1 and 20 in group 2. Intravitreal injections were given in the operating room to all the patients.Povidine iodine 5% drop was instilled in the conjunctival sac. Also 5% Povidine iodine solution was used to clean the eyelid and adnexa and eye draping was done. All Intravitreal injections were done under topical 0.5% Proparacaine anaesthesia maintaining all aseptic and antiseptic measures. Injection was given through the pars plana route approximately 3.5mm-4mm posterior to the limbus in temporal quadrant directly into vitreous cavity with a 30- gauge needle.

Group 1 patients received 1.25 mg of Intravitreal Bevacizumab (Avastin) in a total volume of 0.05ml and Group 2 patients were injected 4 mg of Intravitreal Triamcinolone Acetonide (Triamhexal) in a total volume of 0.1ml. It was given in a slow, steady manner to prevent a sudden flux through the vitreous cavity. Pad and Bandage was done for 4 hours after instillation of Moxifloxacin eye drop. Oral Acetazolamide(250mg) tablet was instructed BD for 2 days to each patient to decrease the chance of IOP rise. Patients were instructed to open their pad and bandage after 4 hours and use eye drop Moxifloxacin 4 times a day for 3 days.

All patients were follow-up on day 1,3, 7, 14, 30 after that in 2, 3 and 6 months. Complete Ocular Examination including measurement of BCVA, slit lamp examination, IOP, fundus examination was done in each patient. Macular OCT was done on 15days, 1 month, 2months, 3months and 6 months of follow-up for measuring Central Macular Thickness. Those patients whose vision was not improved were given 2nd and 3rd injections in both the groups after 4 weeks and 12 weeks of 1st injection.

Statistical analysis

All the data were noted on MS Excel sheet and analysed using SPSS 21.0 package (SPSS Inc., Chicago, USA). Differences of Central Macular Thickness between two groups and differences of Best-Corrected Visual Acuity (Snellen visual acuity at 6m was converted into logarithm of minimum angle of resolution log MAR) were calculated with independent t-test. Results of the analysis were evaluated under 95% confidence interval and mean values as mean± SD. The p value <0.05 was considered as statistically significant.

Results

40 eyes of 35 patients, of which 18 females and 17 males were included in the study. The mean age was 25±9.5 years (range 10-45 years). The mean follow-up period was 22.5 weeks (range 14-32 weeks). There were 17 cases of intermediate uveitis, 11 cases of idiopathic anterior uveitis, 4 cases of Bechet's disease, 4 cases of idiopathic posterior uveitis, 3 cases of VKH and 1 case of idiopathic pan-uveitis and vasculitis. Baseline demographic and clinical characteristics at the time of randomization were summarized by IVB and IVTA group in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics of IVB and IVTA group

Characteristics	IVB group	IVTA group	Significance
Patients(35)	16	19	
Eyes (40)	20	20	
Mean age(in years)	25±9.7	25±8.5	0.839
Male : Female	7/9	10/9	0.762
DIAGNOSIS			
Intermediate uveitis	8	9	
Idiopathic anterior uveitis	5	6	
Bechet's disease	2	2	
Idiopathic posterior uveitis	2	2	
VKH	2	1	
Idiopathic pan uveitis and Vasculitis	1	0	

*IVB- Intravitreal Bevacizumab, *IVTA- Intravitreal Triamcinolone Acetonide

There were no significant differences of Best corrected visual acuity, Central macular thickness and age in study of both groups before injection. The differences between pre-injection time and post- injection status of BCVA, CMT and IOP were shown for each group in Table2.

Table 2: Comparison of results of BCVA (log MAR), CMT and IOP in IVB and IVTA group after successive injection

Time	Pre-injection		1 Month		3 Months		6 Months	
Group	IVB	IVTA	IVB	IVTA	IVB	IVTA	IVB	IVTA
BCVA(log MAR)±SD	0.45±13, 0.46±17		0.12±0.08, 0.13±0.08		0.06±0.08, 0.05±0.07		0.03±0.04, 0.03±0.04	
Mean CMT(μ)±SD	311.76±31.35, 298.52±43.18		258.73±29.31, 230.38±31.27		233.37±27.53, 210.47±21.69		227.13±24.93, 197.68±26.58	
P Value comparison			<0.001		<0.001		<0.001	
Mean IOP±SD			18.38±1.97, 21.00±1.63					

*BCVA- Best Corrected Visual Acuity, *CMT- Central Macular Thickness, *Log MAR- logarithm of the minimum angle of resolution, *SD- Standard Deviation

In IVB group the mean of pre-injection BCVA (log MAR) was 0.45±13 and in IVT group was 0.46±17 respectively. The best visual acuities were achieved 1 month after injection in both groups. The mean of BCVA (log MAR) after 1 month improved significantly from baseline by 0.40 in IVTA group ($p<0.001$) and by 0.41 in IVB group ($p<0.001$). In IVB group improvement in Visual acuity was achieved in 16/20 (80%) of eyes and in IVT group was 19/20 (95%). In IVTA group one eye (5%) and in IVB group 4 eyes (95%) had no improvement in visual acuity after 1 month. In 4 eyes of IVB group and 1 eye of IVTA group 2nd dose of injection was given. None of the eyes had developed complications related to injection of drugs.

The mean of Central macular thickness reduction in the IVTA group was from pre-injection time 298.52µ to 230.38µ, 210.47µ and 197.68µ after 1, 3 and 6 months respectively. In IVB group Central macular thickness was 311.76µ in the pre-injection time and decreased to 258.73µ, 233.37µ and 227.13µ respectively.

Intraocular pressure

The mean of maximum increase in Intraocular pressure was 21.00± 1.63mmHg in IVTA group and was significantly greater than that of IVB group which had IOP 18.38±1.97mmHg($p<0.001$). In IVB group 3 eyes had increase in intraocular pressureand in IVTA group 8 eyes had high intraocular pressure. It was controlled with topical and oral anti-glaucoma drugs. There was no change in optic nerve head appearance.

Discussion

Macular edema is retinal thickening due to accumulation of fluids into the extracellular spaces. When fluid accumulates in cystic spaces it is called cystoid macular edema. The volume of extracellular fluid in retina is regulated with inner and outer blood- retina barrier and retinal pigment epithelium pumping action[10]. Increased vascular permeability is the most common cause of cystoid macular edema.

The mainstay of treatment of Cystoid macular edema is anti-inflammatory drugs. Triamcinolone Acetonide isthe most widely used corticosteroid because of it more lipophilic character and prolonged residence time[11]. A single dose of 4mg when injected in vitreous cavity of a non-vitrectomized eye it shows drug concentration for 3 months[12]. Various studies conducted to evaluate the efficacy of IVTA have shown that IVTA 4mg is effective in reducing Cystoid macular edemaand improvement in visual acuity in 50 -70% of patients. Kok et al found that IVTA was effective in reducing Cystoid macular edema with improvement in Best corrected visual acuity in patients <60 years of age but rise in Intraocular pressure was observed in 43% of subjects[13]. Drug related side effects are cataract, high IOP and injection related complications are Retinal detachment, Endophthalmitis and Vitreous haemorrhage.

Chronic intraocular inflammation leads to increased production of inflammatory cytokines which induce VEGF production by Muller cells. Fine et al study found that aqueous VEGF concentration is higher in patients with UveiticCystoid macular edema than those without CME[14]. All these suggested a possible role of anti-VEGF agents in treatment of Cystoid macular edema. Bevacizumab is one of the most commonly used Anti -VEGF drug in ocular disease.Intravitreal injection of this drug causes reduction in Cystoid macular edema and improvement of visual acuity. Side effects include hypertension, arterial thrombi, menstrual irregularity, nephrotic syndrome and GI complications. IVB is associated with lower rate of cataract progression and rise in intraocular pressure. So it can be effective therapy in Uveitic macular edema, in phakic eyes and steroid responders[15].

The comparative study between effects of Bevacizumab and Triamcinolone has been done in few studies. Lavase et al reported that single IVTA in comparison to IVB is more effective for refractory Uveitic macular edema[16, 17]. Soheilian et al showed that in decreasing Cystoid macular edema, IVTA is as effective as IVB[18,19]. They had done follow-up for 9 months and found improvement of Best corrected visual acuity was significant at 12,24 and 36 weeks for IVB group and for IVT group was 24 and 36 weeks.Central macular thickness reduction was observed only in IVT group. Cystoid macular thickness reduction and Best corrected visual acuity improvement were significant in both groups at 4, 12 and 24 weeks compared to the baselines.

In this study, comparisons of both groups also show Cystoid macular edema reduction and Best corrected visual acuity improvement at 4, 12 and 24 weeks. There is no significant difference in Best corrected visual acuity in IVB and IVTA group at 3 and 6 months after injection but Central macular thickness reduction is significant in IVTA group.

Conclusion

Both IVB and IVTA treatments can effectively improve Best corrected visual acuity and reduce Central macular thickness in Uveitic macular edema patients. The reduction of Central Macular Thickness was greater in IVTA group than IVB group. The IVTA group causes increase in intraocular pressure which can be control under anti-glaucoma medications.

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