ORIGINAL ARTICLE

STERILE ENDOPHTHALMITIS AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB FROM A SINGLE VIAL

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ABSTRACT: PURPOSE: To study the occurrence of sterile endophthalmitis in patients undergoing intravitreal Bevacizumab for various indications. **METHODS:** A retrospective analysis of case records of patients who developed intense anterior and posterior segment reaction after intravitreal bevacizumab was done in detail. **RESULTS:** Six of the twenty six patients (23%) developed sterile endophthalmitis. There was no growth in repeated culture of aqueous or vitreous samples. All patients showed precipitation of drug in vitreous with resolution of symptoms after 8 weeks of intensive steroid treatment. **CONCLUSION:** Intravitreal bevacizumab can cause sterile endophthalmitis though it is a diagnosis of exclusion. In view of many complications a larger clinical trial of intra vitreal bevacizumab is the need of the hour to justify its use.

KEYWORDS: Sterile, Endophthalmitis, Intravitreal, Bevacizumab.

INTRODUCTION: Sterile endophthalmitis after intravitreal injections has been reported in earlier literature and seems to develop mainly in the context of the off-label use of drugs that have not been conceived for intra vitreal administration. The etiology of sterile endophthalmitis, independently of the administered drug, remains uncertain and a multi factorial origin cannot be discarded. Sterile inflammation secondary to intravitreal Bevacizumab has presented as acute and painless vision loss present in the big majority of the cases. Dense vitreous opacity is a common factor, while anterior segment inflammation appears to be mild to moderate. In eyes with sterile endophthalmitis, visual acuity improves progressively as the intraocular inflammation reduces.[1] Despite the advances in the recent diagnostic modalities sterile endophthalmitis should be a diagnosis of exclusion because of the devastating visual prognosis an intraocular infection may cause if left untreated. We are reporting a series of cases which developed severe vitritis and anterior segment inflammation and were repeatedly culture negative which responded to intensive steroid therapy.

MATERIALS & METHODS: This is a retrospective analysis of case records of a total of 26 patients with various etiologies ranging from vein occlusion with macular oedema to diabetic macular oedema and CNVM received intravitreal Bevacizumab from the same vial on the same day under strict aseptic precautions in operation theatre at Vitreo-Retina services department, Minto Ophthalmic Hospital, Bangalore. 6 of 26 developed sterile endophthalmitis had 3 males and 3 females in the group. The age varied from 38 to 54 years among males and 38-53 years among females.

RESULTS: Six of the 26 patients developed sterile endophthalmitis. Of these 3 were males and 3 females. 3 patients who received intra vitreal Bevacizumab had vein occlusion with macular oedema, one had traumatic CNVM, one had moderate NPDR with CSME, and one had myopic CNVM. Two of the five patients had previously received intra vitreal Bevacizumab for traumatic CNVM within a span of three months

A series of six of these patients who were stable on first three days following injection subsequently developed intense anterior uveitis and vitritis. One patient had severe vitritis with worsening of vision required pars plana vitrectomy on day 7 after injection. Two patients had to undergo pars plana vitrectomy and all received multiple intra vitreal antibiotics. None of the gram stain or culture reports of aqueous and vitreous were positive in any of these patients. The culture of bottle and remaining drug of the vial did not show presence of micro-organisms on staining or culture.

All patients showed drug precipitates with complete posterior vitreous detachment. One patient with CNVM developed intense anterior and posterior uveitis which resolved after steroid therapy had hypopon on day one.

DISCUSSION: The incidence of sterile endophthalmitis has been described between 0.09% and 1.1% of IVB injections.[2,3]

None of our patients had pain or chemosis or any such sign of infective endophthalmitis. A presumptive diagnosis of endophthalmitis was made and all patients received multiple subconjunctival and intravitreal vancomycin, ceftazidime injections but showed no response for two weeks. There was posterior vitreous detachment in all patients. One patient had hypopyon which resolved in two days after treatment. Repeated aqueous and vitreous tap of patients did not show presence of bacteria or fungi. Two of the six patients underwent pars plana vitrectomy. The aqueous or vitreous culture for bacteria or fungi remained sterile.

These patients were administered oral and topical steroids in consultation with physician. There was dramatic improvement from the second week itself. Vitritis showed signs of resolution on B- scan. Visual acuity bettered after about a week of oral and topical steroid response. There was complete posterior vitreous detachment in five patients after about four weeks of intensive treatment. All the patients showed precipitation of drug particles after six weeks which eventually started clearing. The patients improved after eight weeks of intra vitreal bevacizumab possibly due to sterile endophthalmitis.

Bevacizumab is a full-length humanized monoclonal nonselective antibody against vascular endothelial growth factor approved by the US FDA for the treatment of colorectal cancer and kidney cancer in combination with chemotherapy. Rosenfeld et al. described for the first time the use of intravitreal bevacizumab (IVB) for the treatment of macular oedema secondary to retinal vein occlusion and exudative age-related macular degeneration.[4]

The safety and efficacy of intravitreal injections depends not only on the surgical technique, but also on the characteristics of the administered drug. The most feared and potentially devastating complication of intravitreal injections is endophthalmitis. Once the diagnosis of acute infectious endophthalmitis is suspected, vitreous tap for microbiological study

and administration of intravitreal antibiotics must be done, while pars plana vitrectomy will have to be performed in many patients.[5]

In our observation 100% of the patients presented with blurred vision, redness, floaters and had signs of anterior segment inflammation in 50% on day 3 and 100% of vitreous inflammation on day 6.

Similar report of 44 cases observed by Chong et al.[6] showed blurred vision was present in 73% of the patients, floaters in 43%, and pain in 34%. Most of the patients had signs of inflammation in vitreous cavity (80%) as well as in the anterior chamber (77%).

Improvement in mean visual acuity of 5 of the six patients was observed after about 90 days of the injection, much longer than what has been reported by various studies quoted by Joaquín et al (37-71 days).[1]

One patient who had developed hypopyon had previously received two doses of intra vitreal Bevacizumab for traumatic CNVM and another patient with myopic CNVM did not show hypopyon but had intense inflammation. As Bevacizumab is a full-length humanized IgG antibody, repeated injection might increase the risk of sterile endophthalmitis. Wickremasinghe et al have reported 19 cases of inflammation after IVB have suggested the possibility of contamination with trace endotoxin of a level not sufficient to cause any signs when administered systemically, might have resulted in the intraocular inflammation. In our study, 2 eyes had prior IVB injections which developed this inflammation. Though it was clinically impossible to differentiate a infective etiology from this entity, early detection and control of inflammation with steroids may help in faster recovery and limit disability.

Bevacizumab generally is well tolerated when administered systemically. Bevacizumab associated infusional reactions are rare, with less than 3% observed in a clinical trial setting; severe reactions were noted in 0.2% of patients. Reactions included hypersensitivity, fever, hypertension, hypertensive crisis etc have been reported in literature.[8] But the possibility of a delayed hypersensitivity reaction after intra vitreal injection cannot be ruled out in view of this inflammation occurring in eyes which had received previous intra vitreal bevacizumab.

Acute intraocular inflammation (or 'sterile endophthalmitis') is a more serious ocular adverse event, but rarely occurs. At 24-months, the CATT trial reported only two cases of 'pseudo-endophthalmitis,' one case in the bevacizumab group and one case in the ranibizumab group.[9] It is still unclear if either bevacizumab offers a safety advantage to the patient. Recently a series of cluster endophthalmitis was reported elsewhere in India.[10]

CONCLUSION: In conclusion, Intra vitreal injection of anti VEG-F agent Bevacizumab may cause sterile endophthalmitis and the course may be as devastating as any other infective etiology. Though it's a diagnosis of exclusion, it requires early detection and intensive anti-inflammatory treatment to avoid sequelae.

Sl. No	Age	Sex	Etiology	Dose	V/a
Case 1	50	M	Branch retinal vein occlusion+macular oedema	1	6/60
Case 2	54	M	Branch retinal vein occlusion+macular oedema	1	6/60
Case 3	53	F	Branch retinal vein occlusion+macular oedema	1	Cf-2m

Case 4	38	F	Myopic cnvm	2	6/36
Case 5	43	F	Moderate npdr + csme	1	6/60
Case 6	38	M	Traumatic cnvm	2	6/60

Table 1

Sl. No	Day 1	Day3	Day 7	1 month	6 months
Case 1	6/60	HM	HM	CF 3M	6/36
Case 2	6/60	PL	HM	CF2M	6/24
Case 3	Cf-2m	CF-CF	CF1M	CF 3M	6/60
Case 4	6/36	CF-CF	CF2M	6/60	6/24
Case 5	6/60	HM	CF1M	6/60	6/24
Case 6	6/60	PL	CF1M	CF2M	6/18

Table 2: after injection visual acuity

CF- COUNTING FINGERS CLOSE TO FACE; HM- HAND MOVEMENTS;

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