Central Retinal Artery Perfusion following 0.1 ml Intravitreal Injection of Bevacizumab

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Abstract

***Purpose*:** To study the pattern of perfusion of central retinal artery (CRA) after 0.1 ml intravitreal injection of bevacizumab to verify the need for any maneuver to decrease the intraocular pressure (IOP) including anterior chamber paracentesis (ACP)

***Methods*:** This is a prospective, interventional, noncomparative case series. Patients receiving intravitreal injection of bevacizumab for choroidal neovascularization (CNV) secondary to age-related macular degeneration, diabetic macular edema and retinal veno-occlusive diseases were included in the study. Each eye received 0.1 ml intravitreal injection of bevacizumab and the status of perfusion of CRA and its pulsation was monitored by indirect ophthalmoscopy until cessation of visible pulsation. Main outcome measures were patency of CRA, its pulsation and time from injection to cessation of pulsation.

***Results*:** Seventy seven eyes of 70 patients were studied. At first ophthalmoscopy 30 seconds after injection, CRA was open in all cases with or without pulsation. CRA occlusion was not observed in any case. In 20 eyes (26%) CRA was patent without pulsation. In 57 eyes (74%) CRA pulsation was detected and this visible pulsation of CRA stopped within an average time of 167±99 seconds (range: 30-480 seconds). From 17 eyes which had significant vitreous reflux, only 6 eyes had CRA pulsation which stopped in a mean time of 80±36 seconds. There was a significant difference between pulsation duration in patients with and without vitreous reflux (Mann-Whitney U test, P=0.005). Absence of postinjection vitreous reflux was a risk factor for CRA pulsation after intravitreal injection of 0.1 ml of bevacizumab (relative risk: 2.41, 95% CI: 1.25-4.62).

***Conclusion*:** Considering the absence of CRA closure and the short time needed for the cessation of pulsation after intravitreal injection of 0.1 ml bevacizumab, no treatment including ACP is warranted before or after such injections in nonglaucomatous eyes. Indirect ophthalmoscopy is a noninvasive useful maneuver to ascertain patency of CRA after intravitreal injections.

***Keywords*:** Intravitreal Injection, Central Retinal Artery, Intraocular Pressure

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Introduction

Intravitreal injection of various pharmacologic agents has gained increased popularity in recent years. It is an extremely efficient method of drug delivery in which the drug is placed directly inside the eye in close proximity to intraocular tissues, specially the posterior segment. Triamcinolone acetonide has been used extensively for treatment of different diseases including age-related macular degeneration, diabetic macular edema, and central and branch retinal vein occlusion.[1-7] Usually a 4 mg dose in 0.1 ml of triamcinolone acetonide is intravitreally injected. With the advent of ocular anti-angiogenic therapies, the number of such injections has been increased to an unprecedented level. Currently, the most frequently used ocular anti-angiogenic agents are bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA, USA) which is a humanized recombinant monoclonal IgG antibody against vascular endothelial growth factor (VEGF) and ranibizumab (Lucentis, Genentech Inc.) which is the Fab portion of the same parent IgG molecule. The originally suggested dose of bevacizumab which is most frequently used at present is 1.25 mg (0.05 ml).[8] However 2.5 mg (0.1 ml) dose is also frequently used.[9,10] There are some reports of combination therapy with 1.25 mg / 0.05 ml avastin plus 2 mg / 0.05 ml triamcinolone acetonide totaling to a 0.1 ml injection volume.[11,12]

One of the side effects of intravitreal injections is immediate increase of intraocular pressure (IOP) due to the increased volume of the globe contents. The magnitude of immediate IOP rise after 0.1 ml intravitreal injections, its consequences, and the way to manage it, have been matters of debate. The main concern about such a pressure elevation is the possibility of central retinal artery (CRA) occlusion. Some investigators[13] have recorded pressure elevations as high as 40.6 mmHg or more and have recommended anterior chamber paracentesis (ACP) to prevent CRA closure. Also some authors[14] believe that even short-term disturbance of retinal circulation may have a deleterious effect on these eyes which may already have compromised circulation due to old age, atherosclerosis and diabetes. Therefore they suggest routine ACP. Others[15-17] have recorded lower postinjection IOP rises and believe that routine treatment for high IOP including ACP is not warranted. On the other hand, ACP as performed by many surgeons is an added procedure which may increase the chance of endophthalmitis,[18] infectious keratitis,[19] iris and lens trauma and anterior chamber hemorrhage. The aim of this study is to assess CRA perfusion after 0.1 ml intravitreal injection of bevacizumab to verify the possibility of its temporary closure and the need for any treatment including ACP.

Methods

This study is a prospective, interventional, noncomparative case series. From March to September 2007 patients who underwent intravitreal injection of bevacizumab (Avastin; Genentech, Inc, made for F. Hoffmann-La Roche, Ltd., Basel, Switzerland) for choroidal neovascular membrane secondary to age-related macular degeneration, diabetic macular edema and macular edema secondary to retinal veno-occlusive diseases were included. Bilateral injections were performed in different sessions and both eyes were included. In cases of repeated injections for one eye, only one of the injections was included.

Exclusion criteria were any history of past or present glaucoma, use of anti-glaucoma medications, opacity of media or inadequate pupillary dilation precluding careful evaluation of the CRA, high myopia with refractive error of more than -6 diopters, previous vitrectomy, history or any signs of episcleritis or scleritis and history of previous corneo-scleral surgery such as scleral buckling, penetrating keratoplasty or pterigium surgery.

The off-label use of bevacizumab (Avastin), possible risks and benefits of the treatment and the observational method used in the study were explained to all patients and those who agreed signed an informed consent. Institutional Review Board/Ethics Committee of Iran University Eye Research Center approved the study.

Before injections, pupillary dilation was achieved with instillation of tropicamide 1% (Sina Darou, Tehran, Iran) two times, 5 minutes apart and phenylephrine 5% (Sina Darou, Tehran, Iran) once. For topical anesthesia tetracaine 0.2% (Sina Darou, Tehran, Iran) eye drop was used. After

prepping the eyelids with povidone iodine 10%, a lid speculum was inserted and few drops of povidone iodine 10% were instilled onto the bulbar conjunctiva and cul de sac. Bevacizumab was pulled into an insulin syringe and needle was changed. In all cases 0.1 ml of bevacizumab (2.5 mg) was injected into the vitreous cavity using a 30 gauge needle, 3-4 mm from inferotemporal limbus. Conjunctiva was displaced with a sterile cotton applicator from the injection site before the injection. The cotton tipped applicator was placed besides the injecting needle and was immediately rolled over the injection site after needle withdrawal and kept in place for 30 seconds by an assistant. During this time, the surgeon placed an indirect ophthalmoscope on his head. After 30 seconds, when the cotton applicator was removed, if there was a leaking bleb larger than about one millimeter in largest diameter, the case was designated as significant vitreous reflux. At this time, the fundus was observed by indirect ophthalmoscope to control the CRA perfusion. If the CRA was open with apparent normal color of disc and retina and without pulsation, a gentle pressure was applied by finger on the globe to induce arterial pulsation in order to ascertain its patency. If the CRA was pulsating after the first 30 seconds, this was an indicator that IOP was raised to a level above the diastolic blood pressure in CRA but yet below the systolic pressure. No treatment was instituted and indirect ophthalmoscopy was repeated every 30 seconds until there was no detectable pulsation of CRA. The interval between injection and cessation of pulsation was recorded for each eye. At the conclusion of the ophthalmoscopy a drop of povidone iodine 10% was instilled into the inferior fornix and a light patch was applied. The patients were discharged home and instructed to remove the patch after three hours and to put betamethasone eye drop every 4 hours for two days in case of itching, burning or irritation. The patients were informed about any possible signs of endophthalmitis and visited the next day. The rest of follow-ups were performed as per routine.

The data were entered into SPSS software (SPSS for windows 15.0, Chicago, IL, USA). Descriptive statistics including mean, standard deviation and range were applied to obtained data. Mann-Whitney U test was used to assess the presence of vitreous reflux from injection site on CRA pulsation duration. Chi-square test was used to assess the effects of various factors on the presence of CRA pulsation.

Results

Seventy seven eyes from 70 patients were included. Forty patients were male (57.1%) and 30 patients were female (42.9%). Mean age of the patients was 64±11.25 years (range: 31-87 years). Thirty six injections were performed on the right and 41 injections on the left eyes. Seventeen patients had significant vitreous reflux from injection site after withdrawal of the needle (22.1%). In no case occlusion of CRA was observed at the time of initial ophthalmoscopy (30 seconds after injection) as evidenced by pale disc and retina and lack of spontaneous pulsation or induced pulsation with digital pressure. At the time of first indirect ophthalmoscopy, 30 seconds after injection, in 20 eyes (26%) CRA was open without obvious pulsation. In 57 eyes (74%) CRA pulsation was detected and this visible pulsation of CRA stopped from 30 to 480 seconds (mean±SD: 167±99 seconds). In the subgroup of eyes without significant vitreous reflux (60 eyes, 77.9%), the mean pulsation time was 177±99 seconds. In the eyes with significant reflux (17 eyes, 22.1%), only 6 eyes had CRA pulsation which stopped in an average time of 80±36 seconds. There was a significant difference between pulsation duration in patients with and without vitreous reflux (Mann-Whitney U test, P=0.005). The number of the eyes with pulsating CRA was significantly higher when significant vitreous leakage was present (P=0.000, Fisher's exact test) (Table 1).

Absence of postinjection vitreous reflux was a risk factor for CRA pulsation after intravitreal injection of 0.1 ml of bevacizumab (relative risk: 2.41, 95% CI: 1.25–4.62). There was no significant association between pulsation time and patient's age, sex and diagnosis.

Table1. Central retinal artery pulsation and effect of vitreous leakage on it in 77 eyes receiving intravitreal injection of bevacizumab

	Significant vitreous leakage 17 eyes (%)	No Significant vitreous leakage 60 eyes (%)	Fisher's exact test
Pulsating central retinal artery	6/17 (45%)	51/60 (89.5%)	P= 0.000
Central retinal artery open without pulsation	11/17 (55%)	9/60 (10.5%)	

Discussion

This is the first report studying perfusion of CRA after 0.1 ml intravitreal injection of bevacizumab in a large series of patients. Although previous studies using intravitreal injection of 0.1 ml triamcinolone acetonide have been published[4-6] and the pattern of increase and normalization of IOP have been demonstrated in some,[13,15,16] the status of CRA perfusion has not been described. The main reason for this may be that triamcinolone acetonide initially makes the media partially opaque and also may precipitate on the posterior pole and optic disc precluding visualization of CRA.

There has been a difference of opinions regarding the necessity of ACP and other maneuvers to counteract the immediate IOP rise after 0.1 ml intravitreal injections. Some authors recommended performing ACP before or after such injections,[13,14] while others may do it if deemed necessary[6] or if the postinjection IOP exceeds 25 mmHg.[20] Some prefer ocular massage[21] or the use of Honan balloon[22] to lower the IOP before the injection. Kotliar et al[13] measured the ocular pressure immediately after 0.1 ml injection of triamcinolone acetonide with Schiötz tonometer and recorded an average postinjection pressure of 57.9±11.4 mmHg. They also developed a biomechanical model relying on three dimensional elasticity theories and their calculation regarding the effect of adding 0.1 ml volume to such a model led to comparable results. They recommended that ACP be performed liberally. Lin and colleagues[14] recommended routine ACP before 0.1 ml injections to avoid damage to optic nerve and ischemic damage to the retina as a result of short-term rise of IOP considering that many of the injected eyes were already affected with retinal vascular diseases. They preferred preinjection ACP to avoid vitreous reflux and also to prevent any postinjection pressure rise. Other investigators believe that ACP and other measures are not generally needed after 0.1 ml injections. Benz et al[15] measured the IOP after 0.1 ml intravitreal injection of triamcinolone acetonide (IVTA) with Goldman applanation tonometer immediately after injection and at 2, 5, 10, 20, and 30 minutes after injection in 38 consecutive patients. Their patients who did not have vitreous reflux had a mean IOP of 45.9 mmHg immediately after injection which rapidly normalized to 20.8 mmHg 20 minutes after the injection. The patients who had vitreous reflux had either no change or a small drop in their IOPs. Based on their findings they commented that after such injections, routine treatment of the patients with ACP or medications is not warranted. They believe that in cases of pain, nausea or continued absence of light perception, the patients may be treated with IOP-lowering medications or, rarely, ACP.

Chang and Chung[17] compared the IOP in two groups, each of 15 patients, receiving 4 mg / 0.1 ml intravitreal triamcinolone. In one group ACP was performed after injection and IOP was measured in both groups at 2, 15, 30 and 60 minutes. The 2-minute postinjection IOP was 7.8±1.46 mmHg and 46.73 with and without ACP respectively. There were no significant differences between the two groups 15 minutes after the injection. They concluded that routine anterior chamber tap is inappropriate due to brief elevation of IOP after such injections. Baath et al[23] retrospectively reviewed the safety profile of IVTA injection in 223 eyes and reported a single case (0.3%) of temporary CRA occlusion which was immediately managed with ACP. Dwinger et al[16] measured the IOP of 32 eyes of 32 patients by applanation

tonometery at 10 minutes and 1, 3 and 24 hours after 4 mg /0.1 ml IVTA injection. The mean postinjection IOP was significantly higher at 10 minutes (22 mmHg) but not thereafter. They concluded that there is a moderate transient rise of IOP after 0.1 ml intravitreal injections and routine paracentesis before or after the injection is not required.

This study showed that after 0.1 ml intravitreal injections in nonglaucomatous eyes, CRA is generally not occluded 30 seconds after intravitreal injection, with or without vitreous reflux. Even if a brief period of CRA occlusion occurs in rare cases, it is unlikely to have any deleterious effect even in eyes with partially compromised vasculature. Hayreh and Jonas[24] showed that in middle age and elderly atherosclerotic and hypertensive rhesus monkeys, occlusion of CRA for less than 100 minutes produce no apparent morphometric evidence of nerve fiber layer and optic nerve damage. Therefore we believe that ACP or other treatments are generally not necessary after such injections in nonglaucomatous eyes.

Another advantage claimed for preinjection ACP[14] is that it reduces vitreous reflux and therefore helps to keep all the medication inside the eye. In our patients only 22% of the eyes had significant reflux. It should also be considered that the reflux fluid consists of liquid vitreous mixed with medication and it is unlikely that a significant amount of the medication that is injected into the center of the vitreous cavity exits from the puncture site. Considering that the injection site is located in the pars plana and vitreous base area, it seems that any amount of vitreous reflux (whether slight or significant reflux) that usually occurs after intravitreal injections does not have significant deleterious consequences on retina.

To the authors' knowledge, this is the first study demonstrating the pattern of perfusion of CRA after 0.1 ml intravitreal injections. In this study we did not measure the IOP after intravitreal injections for two reasons. First, the pattern of immediate increase and normalization of the IOP after 0.1 ml intravitreal injections has been previously well described.[13,15] Second, the main significance of immediate rise of IOP is that it may compromise arterial circulation and that has been our main outcome measure.

This study has some limitations. The first ophthalmoscopy was performed 30 seconds after the injection. It is possible that there have been closure of CRA for shorter time than 30 seconds in some eyes. However, as stated earlier, such short-term cessation of blood flow is unlikely to have any significant deleterious effect. Also we performed indirect ophthalmoscopy every 30 seconds and not continuously, fearing the harmful effect of continuous bright light on the posterior pole. So the time periods for cessation of arterial pulsation may have inaccuracies in the order of few seconds.

Conclusion

In conclusion, this study demonstrated that after 0.1 ml intravitreal bevacizumab injection, CRA occlusion typically does not occur for any significant period of time. With a 30 G needle, 22% of the eyes had significant reflux. In eyes without significant leakage, 74% had visible pulsation which disappeared within a mean time of 3 minutes. In eyes with significant reflux, CRA pulsation disappeared within 80 seconds on average. Even if a brief occlusion occurs in rare cases it is unlikely to result in permanent retinal or optic nerve head damage. On the other hand, ACP is an invasive procedure which may increase the chance of endophthalmitis[18] and damage to the iris and lens. Therefore, we don't recommend routine ACP or any other therapeutic maneuver to decrease IOP after 0.1 ml intravitreal injections in nonglaucomatous eyes. Indirect ophthalmoscopy is a useful noninvasive tool which enables the surgeon to ascertain patency of the CRA after each intravitreal injection.

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