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The Effect of Avastin on Posterior Capsular Opacification after Phacoemulsification: A Randomized Controlled Trial Mitsugu

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Abstract

Background: Cataracts are a leading cause of visual impairment in people. Phacoemulsification with intraocular lens (IOL) implantation is the predominant procedure performed for restoration of vision. Highly effective immediate restoration of vision gradually declines due to the development of posterior capsule opacification (PCO). The aim of this study is to compare the success rate of bevacizumab *vs.* placebo for prevention of PCO following phacoemulsification

Materials and Methods: In this double blind randomized clinical trial, thirty patients (60 eyes) underwent cataract extraction by phacoemulsification. 30 eye's received Avastin in the form of injection between the IOL and posterior capsule (Study group) while 30 eyes were injected BSS (Control group) in the same manner after phacoemulsification. Complete ophthalmic examination including tonometry (IOP, intraocular pressure), visual acuity (VA) and posterior capsule evaluation was done in follow up periodic and PCO densitometry with Pentacam was done in the last follow up (1year). The comparisons were done with Wilcoxon matched pairs test, chi square test and independent samples t-test. Statistical significance was considered at $P<0.05$.

Results: We identified 113 trials, consisting of 39 positive and 74 negative trials (overall success rate: 35%). Most of the primary endpoints (77%) were progression-related or recurrence-related. The success rates of trials assessing progression-related and recurrence-related endpoints were 39% and 17%, respectively. Progression-related and recurrence-related endpoints in the control arm showed significant improvement, compared with pre-trial estimates, which were associated with negative results.

Conclusions: Bevacizumab (Avastin) is not more effective than placebo for prevention of PCO following phacoemulsification. However, more studies with greater patient number are suggested.

Keywords: Posterior capsular opacification; Avastin; Phacoemulsification

Introduction

Cataract is an ocular disease that is known to interfere with protein nature and crystalline lens function. This is due to the turbidity and structural deformation of the crystalline lens in the patients [1,2]. Various methods are used for cataract surgery and one of the most advanced methods, is modern extracapsular cataract extraction surgery which involves removal of the lens fibers, that form the nucleus and cortex of the crystalline lens, leaving the posterior epithelial capsule to hold the new artificial intraocular lens (IOL) and keep the vitreous humor away from the anterior chamber. Extracapsular techniques of cataract extraction surgery originally involved manual nuclear expression. Phacoemulsification is a mechanically assisted extracapsular technique of cataract extraction surgery [3]. One of the common complications of cataract surgery, particularly in extra-capsular surgery is posterior capsular opacification. The posterior capsule opacification (PCO) begins in the course of several months to several years after cataract surgery and progresses gradually [4]. PCO is the most common postoperative complication of cataract surgery. It is supposed that residual lens epithelial cells are inevitably left at surgery in the equatorial capsular bag. PCO is caused by lens epithelial cells that remain in the capsular bag after cataract surgery, they migrate, proliferate and transform to produce Elschnig's pearls and capsular fibrosis [5-8]. Different methods have been proposed for the prevention and treatment of PCO, which in many cases did not have a proper effect, such as complicated and aggressive capsulotomy. Recently, vascular endothelial growth inhibitors have been suggested to prevent PCO. Avastin® (bevacizumab), is a monoclonal antibody, and widely used in more than 20 types of ocular pathology [6-9]. Some previous studies are more specific to diabetic patients and show efficacy of bevacizumab. Therefore, we report regression of PCO after Cataract surgery in non-diabetic patient following Avastin injection. The rationale for doing this study is that suppression of neovascularization cascade with anti-VEGF drugs can influence inflammatory and pre-inflammatory cytokines such as FGF (fibroblast growth factor) and EGF (Epidermal growth factor) with resultant decrease in fibroblast proliferation and ensuing fibrosis (which leads to PCO) [10-20]. this is the first study, evaluating the efficacy of Avastin in no diabetic patients.

Materials and Methods

Thirty patients (17 men and 13 women) with bilateral cataract were evaluated in the current study in the, Nikookari Eye Hospital. Each patient with bilateral cataract, who was candidate for operation, underwent phacoemulsification surgery. The study was designed as double-blind style and the power of the test was 0.8 which means the model will reject a false null hypothesis with 80 per cent probability. Using simple randomization procedures, patients were randomly assigned to inject either Avastin or BSS (balance sodium solution). Written informed consent was obtained from all patients and the study was approved by the Tabriz University of medical sciences local ethics committee. Participants did not receive a stipend.

The inclusion criteria were 40+ years of age, bilateral cataract, informed consent of patients to participate in the study and the exclusion criteria were diabetes mellitus, previous history of ocular surgery, previous history of the ocular trauma, history of uveitis, systemic underlying disease. Preoperative evaluation included medical history and complete ophthalmologic examination, including uncorrected visual acuity (UCVA), intraocular pressure (IOP) evaluation, ophthalmoscopy.

All patients operated bilaterally with one-month interval, one eye of each patient was randomly selected for Avastin injection and the other eye of the same patient received BSS. The pre-operative evaluation included: complete medical history, full ophthalmology, IOP measurements, visual acuity (VA), corrected distance visual acuity (CDVA) and Uncorrected visual acuity (UCVA), and recorded in a special checklist. In order to avoid any risk of bias, both eyes were matched in terms of primary intraocular pressure and visual acuity. The surgeon was aware of the intervention but the examiner was not. After anesthesia, a 3-mm temporal clear corneal incision was made with a diamond knife. Lens extraction was performed by phacoemulsification using the quick chop technique. After ensuring complete cortical removal by automated irrigation–aspiration, in all cases, intraocular lens (MI60) bausch and lomb lens was implanted in the capsular bag. After the phacoemulsification was completed, 1.25 mg/0.1 cc Avastin (bevacizumab 100 mg/4 ml, Roche/Swiss) or 0.1 cc BSS (placebo) was injected between IOL and posterior capsule in the posterior chamber. The patients were evaluated on the 12 month after the surgery. Complete ophthalmologic examination including VA, intraocular pressure, and detailed slit-lamp biomicroscopy specially the degree of PCO with red reflex and retroillumination under maximal midriasis was repeated in each visit. At the end of one year, all patients after midriasis with administration of 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P), Scheimpflug images were obtained using the Scheimpflug device and anterior-segment Pentacam (oculus/Germany) analyzer. For the PCO evaluation group, 3 images at 60, 120 and 180 degrees were analyzed cross-sectionally and the total average calculated in the central 3 mm [7].

All aspects of the Helsinki Declaration for the protection of human subjects in research studies were followed. Statistical analysis was performed using SPSS 22.0 software (SPSS Inc., Chicago, Illinois, USA). Normality of all values was confirmed using Wilcoxon test. The comparisons were done with the chi-square test for categorical variables, and independent samples t-test for continuous variables. A P value less than 0.05 was considered statistically significant. The changes in the posterior capsule opacity, VA and fibrosis were evaluated again and were compared with the follow and the same eye in one year earlier.

Results

30 patients underwent bilateral cataract surgery; 3 patients were excluded during follow up period due to lack of cooperation. Finally, from 27 patients, 17 (63%) were male, and 10 (37%) were female. The mean age of patients was 63 ± 11 years ranging from 44 to 83 years. The mean age of males was 64.05 ± 12.56 years and the mean age of females were 61 ± 11 years. There was no significant difference between men and women in terms of mean age (P=0.064). Two groups were matched for visual acuity, intraocular pressure, and laterality of the recipient's eyes, it means; there was no significant difference between two groups (P>0.05). The patient's visual acuity (UCVA) means in the placebo group and the Avastin group was showed in Table 1, VA reported with Decimal Notation. Finally, in clinical examinations after surgery, the clinical characteristics of each group eyes were evaluated. After surgery the Visual acuity without correction was significantly improved in both groups, it means there is a significant difference between preoperative visual acuity and postoperative visual acuity (P<0.05). The visual acuity of the patients in the placebo group was in the range of (0.05 to 0.9) and the Avastin group was in the range of 0.2 to 1 (Table 2).

Group	Mean ± Std. Deviation	Minimum	Maximum
V/A (Placebo)	0.33 ± 0.28	0.05	0.8
V/A (Avastin)	0.34 ± 0.24	0.05	0.8

Table 1: Uncorrected VA in two groups before operation.

Group	Mean ± Std. Deviation	Minimum	Maximum
V/A (Placebo)	0.64 ± 0.26	0.05	0.9
V/A (Avastin)	0.64 ± 0.23	0.2	1

Table 2: Uncorrected VA in two groups after operation.

At the end of the study, visual acuity demonstrated no statistically significant difference between two groups (P>0.05). In specific examinations after phacoemulsification cataract surgery in non-diabetic subjects, we found the densitometry values of the eyes were slightly decreased in the Avastin group. The posterior capsule opacity of the patients in the placebo group was within the (3.63 to 6.9), also in the Avastin group within the (0 to 6.30) range. The comparison of the results of the densitometry between the two placebo and bevacizumab (Avastin) groups did not show a significant difference (P>0.05) (Table 3).

Group	Mean ± Std. Deviation	Minimum	Maximum
Densitometry (Placebo)	4.44 ± 0.68	3.63	6.9
Densitometry (Avastin)	4.14 ± 1.08	0	6.3

Table 3: Eyes densitometry after operation.

At the end of the study, the comparison of the effect of bevacizumab (Avastin) and BSS (placebo) on phacoemulsification in non-diabetic patients demonstrated no evidence of beneficial effects of bevacizumab (Avastin) on PCO.

Discussion

The PCO is increasing in the worldwide which is a major problem after cataract surgery; the problem is most patients expect a complete recovery of VA after cataract surgery, but they face with vision reduction followed by PCO after it [10-12]. Another problem caused by PCO is that a delayed diagnosis can lead to incurable amblyopia in children. Also, the PCO, even at low levels, can distort vision in those who have multifocal IOLs and affect the lens adaptation in them. The PCO treatment is high costly and posterior capsulotomy in patients with high myopia, or uveitis and glaucoma, or diabetic retinopathy can be associated with an increasing risk of complications of the posterior segment [9-14]. Currently, ophthalmologists are investigating on strategies to reduce the PCO followed by cataract surgeries, this reduction is achievable by changing the surgical methods, drugs or toxins which cause the destruction of epithelial cells in lens, and also making some changes in IOL design or materials.

Physically it is not possible to remove all epithelial cells from the capsular bag after the surgery [15-17]. Various studies on tissue level showed that just within a few days after the surgery, the remaining cells completely expanded to the posterior capsule surface, tending to spread throughout the posterior capsule, so that fibrous metaplasia occurs during their growth. Since the extracapsular cataract surgery is accompanied by breaking the blood-aqueous barrier, the inflammatory cells and some chemical intermediates as well as the PMN cells, growth factor, cytokines and fibroblasts access into the aqueous humour [16]. The collagen precipitation on the intraocular lens and the lens capsule causes the posterior capsule to opacity and wrinkle [16,17]. TGF-beta causes abnormal lens cell proliferation; it has been seen that TGF-beta causes opacity of the lens capsule *in vitro* level [17]. These studies indicated that TGF-beta causes some changes in the lens epithelium mesenchymal which lead to fibrotic changes and opacity of the lens capsule [16-20].

Bevacizumab (Avastin) is a humanized, full-length monoclonal antibody that inhibits all isoforms of vascular endothelial growth factor (VEGF). It is approved as an intravenous treatment for metastatic colorectal cancer in February 2004. Several case series have shown promising results for using off-label intravitreal bevacizumab for the treatment of exudative age-related macular degeneration, proliferative diabetic, retinopathy, neovascular glaucoma (NVG), macular edema from retinal vein occlusion, and one single case of posterior capsule neovascularization [17-22]. The hypothesis for doing this study is that suppression of neovascularization cascade with anti-VEGF drugs can influence inflammatory and pre-inflammatory cytokines such as FGF (fibroblast growth factor) , EGF (Epidermal growth factor) and TGF-ß with resultant decrease in fibroblast proliferation and ensuing fibrosis (which leads to PCO) [18-20].

In our study, 54 eyes with cataract were compared within two groups. For the first group, the cataract surgery using the phacoemulsification method was performed and during the surgery bevacizumab (Avastin) injected after the IOL placement between the IOL and posterior capsule, the second group received BSS in posterior chamber. After the twelve months, the mean visual acuity in the first group was not significantly different between the two groups ($P>0.05$). However, according to the examinations and clinical findings, our study showed a significant improvement in postoperative visual acuity ($P<0.05$) in both groups compared to preoperative visual acuity ($P>0.05$). The densitometry performed for each of the eyes to evaluate the opacity of the posterior capsule showed that posterior capsule opacity after receiving Avastin in phacoemulsification surgery in first group was not significantly different in comparison of the second group after receiving the placebo. Statistical comparison of capsule characteristics at the end of follow up period for each of the eyes did not demonstrate any significant difference in the two groups. In either of the two study groups, the placebo and Avastin group did not show any complication after surgery such as hyphema, corneal edema, elevated intraocular pressure, uveitis and IOL displacement.

Conclusion

Based on the present study, the use of bevacizumab (Avastin) in reducing posterior capsule opacity after phacoemulsification cataract surgery in non-diabetic patients was not more effective than placebo. The injection of bevacizumab (Avastin) has not diminished the severity posterior capsular opacity, although it may be effective in diabetic patients. Therefore, the use of bevacizumab (Avastin) in non-diabetic patients who are undergoing phacoemulsification cataract surgery is not recommended. Further studies with greater patient numbers and longer follow-up would be of interest.

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