The Incidence and Surgical Management of Cataractogenic Trauma that is applied to the Crystalline Lens During Intravitreal Injection

İntravitreal Enjeksiyon Esnasında Kristalin Lense Uygulanan Kataraktojenik Travmanın İnsidansı ve Cerrahi Yönetimi

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ABSTRACT

Purpose: The aim of this study is to report on the incidence and management of iatrogenic cataracts caused by needle penetration of the posterior capsule during intravitreal injection.

Material and Methods: 973 phacic patients (1,646 eyes) with age-related macular degeneration who received an intravitreal anti-vascular-endothelial-growth-factor injection were included in this retrospective study. All the 8,764 intravitreal injections were performed in an office setting. After the clinical appearance of cataracts, a phacoemulsification operation was performed on the patients.

Results: Iatrogenic cataracts caused by posterior capsule perforation were identified in three eyes of three patients. One of these three patients was injected with ranibizumab and two patients were injected with bevacizumab. Two of the patients were operated on using the phacoemulsification cataract surgery whereas one patient was operated on with combined phacoemulsification and pars plana vitrectomy.

Conclusion: Despite all the precautions taken and maneuvers applied during intravitreal injection, posterior segment surgery may be needed to treat complications afterwards.

Key Words: Iatrogenic cataract, intravitreal injection, traumatic cataract.

ÖZ

Amaç: Bu çalışmanın amacı intravitreal enjeksiyon sırasında posterior kapsül penetrasyonuna bağlı iyatrojenik kataraktların insidansını saptamak ve bu olgulara yaklaşımı sunmaktır.

Gereç ve Yöntemler: Yaşa bağlı makula dejenerasyonu (YBMD) olan ve intravitreal anti-vasküler endotelyal growth faktör (anti-VEGF) enjeksiyonu yapılan 973 fakik hastanın 1646 gözü bu retrospektif, çalışmaya alınmıştır. 8764 intravitreal enjeksiyonun tümü ofis şartlarında gerçekleştirilmiştir. Katarakt kliniği ortaya çıktıktan sonra bu hastalara fakoemülsifikasyon operasyonu yapılmıştır.

Bulgular: Üç hastanın üç gözünde posterior kapsül perforasyonuna bağlı iyatrojenik katarakt saptanmıştır. Üç hastanın bir tanesine ranibizumab ve iki tanesine bevacizumab enjeksiyonu yapılmıştır. Katarakt ameliyatı yapılan hastaların ikisinde komplikasyonsuz fakoemülsifikasyon cerrahisi yapılmışken bir vakada pars plana vitrektomi ile kombine fakoemülsifikasyon cerrahisi yapılmıştır.

Sonuç: İntravitreal enjeksiyon sırasında alınan tüm önlemlere rağmen sonrasında komplikasyonların tedavisi için arka segment cerrahisi gerekebilir.

Anahtar Sözcükler: İyatrojenik katarakt, intravitreal enjeksiyon, travmatik katarakt.

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INTRODUCTION

Vascular endothelial growth factor (VEGF) has been shown to increase vascular permeability, induce vascular endothelial cell proliferation, promote endothelial cell survival, and serve as a chemotactic factor for leukocytes, thus having all the properties thought to be important for its role as an angiogenic and edematous factor.[1] Thus, intravitreal injections of anti-VEGF agents have become an effective and preferred treatment strategy in neovascular retinal diseases. Since 2005, bevacizumab has been used to treat neovascular age-related macular degeneration (ARMD) and other neovascular retinal diseases, such as proliferative diabetic retinopathy (PDR), central retinal vein occlusion, and retinitis pigmentosa.[2-7]

Intravitreal delivery of these agents is generally well tolerated by the majority of patients; however, their use entails local and systemic complications. Injection related inflammation, traumatic injury to the lens capsule, retinal detachment (RD), vitreous hemorrhage, and endophthalmitis [8-12] are among the reported local complications, and systemic complications include temporary elevation of systolic blood pressure and adverse cerebrovascular events.[13,14] The goal of this paper is to report on the incidence of iatrogenic cataract cases caused by needle penetration of the posterior capsule during an intravitreal injection, as well as our approach to treating them.

MATERIALS AND METHODS

This was a retrospective, non-comparative study of 1,646 eyes of 973 patients who had received at least one intravitreal anti-VEGF injection (bevacizumab, ranibizumab, or pegaptanib) for neovascular ARMD in the ophthalmology department of Istanbul Bilim University. This investigation adhered to the tenets of the Declaration of Helsinki, and written informed consent was given by all participants. The institutional review board of Istanbul Bilim University approved the study protocol. A total of 8,764 intravitreal injections performed at our clinic were retrospectively analyzed by reviewing patient records. All injections were performed by the same surgeon.

Patients were excluded if they had undergone ocular surgery (e.g., phacoemulsification, vitrectomy) in less than a year or if they suffered from chronic ocular disease (e.g., uveitis, optic neuritis), open-angle glaucoma, angle-closure glaucoma or suspected glaucoma, optic nerve disease (e.g., anterior ischemic optic neuropathy) or neurologic disease (e.g., multiple sclerosis).

Intravitreal injections were performed as an outpatient procedure under strict aseptic technique. Local anesthesia was achieved using 0.5% proparacaine (Alcaine; Alcon Laboratories, Inc., Fort Worth, TX, USA), and a 10% povidone-iodine solution was applied to the eyelids and in the conjunctival sac for 5 minutes, followed by draping and insertion of a lid speculum. Intravitreal injections of bevacizumab (1.25 mg/0.05 ml; Roche, Genentech, Inc.), ranibizumab (0.5mg/0.05mL; Lucentis, Genentech, Inc.) and pegaptanib sodium (0.3mg/0.05mL; Macugen, Eyetech/Pfizer) were performed from 4-mm post-limbus in the inferior or inferotemporal quadrant. The needle is advanced into the mid vitreous cavity and visualized through the pupil. The needle was removed simultaneously with the application of a cotton tip over the entry site. Immediately after injection, a 10% povidone-iodine solution was applied to the ocular surface. The optic nerve head was then examined for arterial pulsation to check for complications, and indirect ophthalmoscopy was performed to ensure correct placement of the injection and to evaluate the retina. Tonometry was carried out after the procedure.

In each visit, the visual acuity (VA) of the patients was measured using the ETDRS scale. In addition, the biomicroscopic examination of the anterior segment, the measurement of the intraocular pressure, the fundus examination, and the central macular thickness measurement with optic coherence tomography were employed in each visit. Fundus fluorescein angiography was repeated semi-annually after diagnosis. Posterior capsular rupture was diagnosed with the retroillumination technique.

RESULTS

A total of 8,764 intravitreal anti-VEGF injections were performed to 1,646 eyes of 973 patients between September, 2006 and December, 2015 in our clinic. Of the 8,764 injections, 3,526 were bevacizumab, 5,114 were ranibizumab, and 124 were pegaptanib injections.

We observed three cases of cataract development as a consequence of iatrogenic posterior capsule perforation (Figure 1-3). The incidence of iatrogenic capsular perforation was 0.034% per injection, 0.18% per eye, and 0.30% per patient. One patient was treated with ranibizumab (33.3%), and two were treated with bevacizumab (66.6%) for the treatment of ARMD. Two of the patients had cataracts in their left eyes

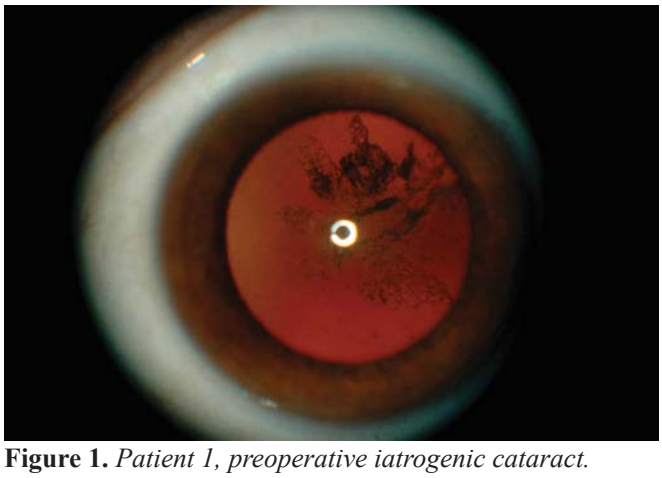

Figure 1. *Patient 1, preoperative iatrogenic cataract.*

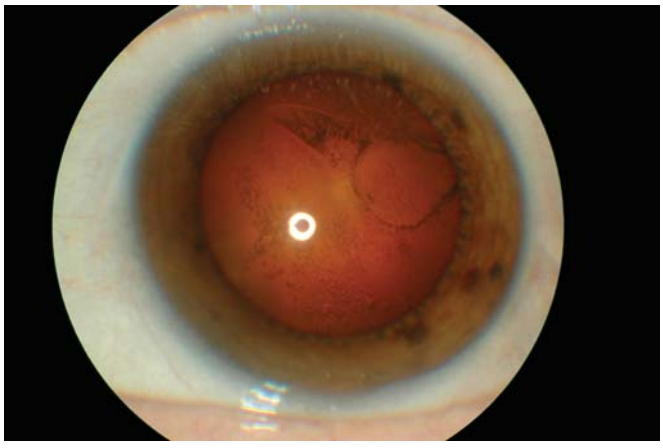

Figure 2. *Patient 2, iatrogenic cataract image, which starts in the upper temporal region and branches out to the central part of the lens.*

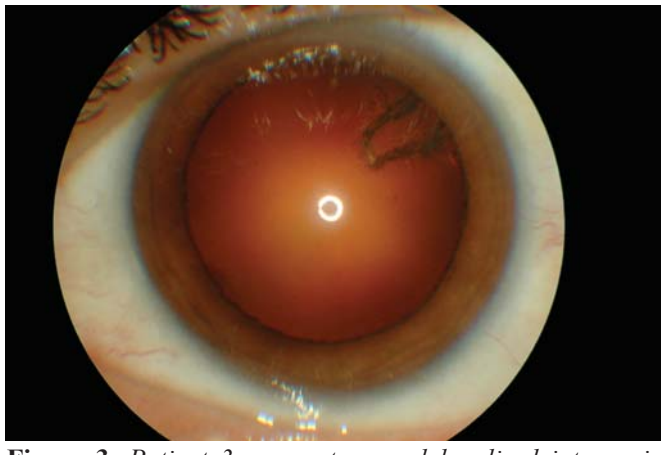

Figure 3. *Patient 3, upper temporal localized iatrogenic cataract image.*

and one of them had cataract in her right eye. Two of these patients were male (66.6%), and one patient was female (33.3%). Results are summarized in Table 1 for all patients, and details of the three patients with iatrogenic cataracts are presented in Table 2. Detection of the posterior capsular perforation and cataract was achieved between 28 days to 58 days post-injection.

Patients' VA before injection were 20/200, 20/125 and 20/200 respectively. Two of the patients underwent phacoemulsification operation, planned anterior vitrectomy and sulcus implantation of foldable three-piece intraocular lens (AcrySof MA60AC, Alcon, Fort Worth TX) and one underwent a combined phacoemulsification and pars plana vitrectomy and transscleral ciliary sulcus fixation of posterior chamber three-piece intraocular lens (AcrySof MA60AC, Alcon, Fort Worth TX). The third patient had no additional risk factors such as pseudoexfoliation or zonular defect.

The VA of the patients before intravitreal injection were 20/200, 20/125 and 20/200 respectively. After cataract formation the VA of the patients were measured as 20/200, 20/100 and 20/250 respectively. After cataract removal, the VA of the patients were 20/100, 20/32 and 20/200 respectively. There were no additional complications after surgeries.

DISCUSSION

Substantial clinical experience with intravitreal injections has provided clinicians with an outline of avoidable risks. Meyer et al. state that because it is an invasive technique, an intravitreal injection can potentially damage three major intraocular structures. A posterior placement may damage the ora serrata or even pass through the neuroretina, inducing a full-thickness retinal tear and consecutive development of a rhegmatogenous RD.[10]

The pathway of the needle normally reaches directly into the vitreous cavity, crossing the pars plana without damaging adjacent structures and the solution is gently injected into the midvitreous cavity. The injection can be done under a microscope, under direct vision, or through an indirect ophthalmoscope based on the surgeon's preference. The depth

Table 1. *Number and percentage of patients and injection types in study patients*

	Ranibizumab	Bevacizumab	Pegaptanib	Total
Patients	549 (56.4%)	392 (40.3%)	32 (3.3%)	973
Eyes	939 (57.1%)	663 (40.2%)	44 (2.7%)	1,646
Injections	5,114 (58.3%)	3,526 (40.2%)	124 (1.5%)	8,764
Iatrogenic Cataracts	1	2	-	3

Table 2. *Details of three patients with iatrogenic cataract*

	Age	Gender	Anti-VEGF	Eye	Day of cataract diagnosis	Treatment
Patient 1	65	Male	Ranibizumab	Left	28	Phacoemulsification
Patient 2	60	Female	Bevacizumab	Right	58	Phacoemulsification
Patient 3	63	Male	Bevacizumab	Left	31	Phacoemulsification +PPV

Table 3. *Patients' visual acuity before intravitreal injection, after cataract formation and after operation.*

	Visual acuity before intravitreal injection	Visual acuity after cataract formation before operation	Visual acuity after operation
Patient 1	20/200	20/200	20/100
Patient 2	20/125	20/100	20/32
Patient 3	20/200	20/250	20/200

of the insertion should be between 5 and 7 mm, the drug should be introduced slowly, and the needle should be removed gently. The needle size should not exceed 27 gauge, and the needle tip should be sharp enough not to indent the insertion point and further narrow the angle between the needle and the lens.[13-16] In our clinic, these basic principles are followed during all injections. On the other hand, lens damage may occur due to the insufficent cooperation of the patient, the inexperience of the surgeon or the anatomic variations in the patients.

The overall incidence of traumatic lens injuries as a complication of intravitreal injection is given as 0.006% (2/32, 318) in Meyer et al.'s two-year multicentric case series.[10] Shima et al. found a lens injury rate of 0.07% (1/1,300) among bevacizumab injections and of 0.14% (1/707) among patients treated.[17] Jonas et al. reported the rate of progressive cataract formation per injection as 0.05% (2/3,818) in their seven-year case series of patients who received bevacizumab injections.[18] Fung et al. conducted an internet based survey to identify adverse events associated with intravitreal bevacizumab treatment and found that one out of 5,228 patients developed cataracts. Fung et al.'s study included a total of 7,113 injections, so their rate of cataract formation is 0.019% per patient and 0.014% per injection.[19] The VISION study comprised 1,186 patients receiving 7,545 intravitreal pegaptanib injections; their traumatic lens injury rate per injection was 0.07% (5/7,545), and per patient it was 0.6% (5/1,186).[20] The overall incidence of cataract formation per intravitreal injection of our clinic is 0.03% (3/8,764), and per patient the rate is 0.30% (3/973). Our study has a large sample size of injections performed in one clinic by one surgeon. These properties should minimize the technical differences between injections or operations, and it should give an accurate incidence of iatrogenic capsular trauma.

In terms of other complications, Meyer et al. gave an incidence of 1 RD per 7,188 injections, whereas in our clinic, there were no RDs after intravitreal injections. This may be due to our anterior placement of the injection, as opposed to posterior placement, which can lead to the development of rhegmatogenous RD.[21] In one of our previous studies, we reported an overall incidence rate of 0.066% (3/3,022) for post-injection culture-proven endophthalmitis, which is consistent with other studies about endophthalmitis rates after intravitreal injections.[7] That study was published in 2009, and it included 3,022 injections. In this study, the number of injections included increased to 5,771, and the number of endopthalmitis cases remained at 3, which is still consistent with other studies.

Operational management of this type of cataract is challenging; capsular integrity is often compromised. The goal during the phacoemulsification procedure is to exert minimal hydrostatic pressure on the lens by using low fluidic parameters and to avoid extending the preexisting capsular

rupture. With lowered fluid flow, there is reduced turbulence within the anterior chamber.[22-25] Thus, the bottle height should be set between 70 and 90 cm (depending on each case), and the surgeon's preferred technique, especially during fragment removal, should be as follows: The irrigation should be in a noncontiniuous mode, the aspiration flow rate should be fixed to 30 mL/min in a noncontinious mode, and the vacuum level should be set to 300–450 mmHg. The key approach in the operation is to apply the hydro-maneuvers in a nonstandard manner. Because of the preexisting posterior capsular tear, the lens is expected to behave like a traumatic cataract or a capsular blowout encountered during hydrodissection. We avoided hydrodissection, which emphasized the hydrodelineation, and used the lens cortex as a protective capsule around the nucleus, where we operated with the phacoemulsification. The technique of avoiding hydrodissection has been mentioned in the literature as well; Saeed et al. used this approach in two traumatic cataract cases secondary to inadvertent needle penetration during an intravitreal injection. They mention the importance of low bottle height for maintaining an acceptable low hydrostatic pressure in the anterior chamber. They also used a dispersive ophthalmic viscosurgical agent (OVD) to avoid the pressure that a cohesive OVD would exert on the lens, thus extending the tear. The most outstanding approach was a careful hydrodelineation without hydrodissection in order to leave a cortex shell above the tear for protection, and they advised avoiding a nuclear rotation for the same reasons.[22]

Kummelil et al. described the use of intraoperative anterior segment OCT to detect a preexisting posterior capsule tear and the appropriate management. In this case report, posterior capsular tear noticed during emulsification of the last nuclear piece which was safely emulsified after an ophthalmic viscosurgical device was injected beneath it. An anterior vitrectomy was done and a 3-piece foldable IOL was subsequently inserted in the sulcus with the optic capture. They emphasized that cataract surgeons should have the necessary anterior vitrectomy equipment and appropriate surgical technique to manage the posterior capsule tears.[26]

The present study included a large sample size in one clinic, and injections were performed by one surgeon, thus minimising the technical differences between injections or op-

erations and providing a completely homogeneous study group. To the best of our knowledge, this study is the first to report pars plana vitrectomy for an iatrogenic cataract case secondary to intravitreal injection. We assume that an iatrogenic cataract should be expected to behave in similar fashion to a traumatic cataract.

In conclusion, despite all the precautions and maneuvers used to perform intravitreal injection, posterior segment surgery may be needed to treat complications. Therefore, these procedures should be managed as an anterior and posterior segment combination procedure. All patients should be informed about iatrogenic cataract formation and its complications for medicolegal responsibility.

Author Disclosure Statement

The authors have no conflicts of interest to declare.

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