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한국인에서 단일 술자에 의한 유리체강내 주사 후 발생한 열공망막박리 발생률 및 임상양상

Incidence and Clinical Features of Rhegmatogenous Retinal Detachment After 9,484 Intravitreal Injections by a Single Physician

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Purpose: To report the incidence of rhegmatogenous retinal detachment (RRD) following intravitreal injections and describe its clinical features.

Methods: The medical records of patients who received intravitreal injections from a single retinal specialist between February 2012 and January 2019 at a tertiary referral-based hospital and who had at least three months of follow-up data were analyzed retrospectively.

Results: In total, 9,484 intravitreal injections were performed by a single physician in 1,739 eyes of 1,480 patients during the study period. The mean patient age was 59.7 years at the time of the first injection. Patients received an average of 5.3 injections per eye during a mean follow-up period of 26.3 months. RRD occurred as a complication in only one case for an overall incidence rate of 0.01% per injection and 0.06% per eye. In that specific case, RRD occurred two weeks after an intravitreal injection, and the retina was successfully reattached without recurrence after prompt vitrectomy.

Conclusions: The observed incidence rate of RRD after intravitreal injection was extremely low, similar to that reported in previous studies.

Keywords: Incidence; Intravitreal injection; Rhegmatogenous retinal detachment

Introduction

Intravitreal injection is a treatment modality adopted widely in many diseases, including exudative age-related macular degeneration (AMD), retinal vein occlusion with macular edema, diabetic macular edema, proliferative diabetic retinopathy (PDR) with vitreous hemorrhage, and choroidal neovascularization secondary to various chorioretinal diseases including central serous chorioretinopathy. Intravitreal injections are reported to be administered 5.6 to 13 times per year on average in patients with AMD [1] and 5.8 times per year in those with diabetic retinopathy [2]. Moreover, the number of patients receiving intravitreal injections is increasing [3,4],

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with most needing to receive continuous treatment to maintain the therapeutic efficacy. Many studies have sought to discern the best way to minimize the various potential side effects of intravitreal injections [5-7], but severe complications continue to appear, including endophthalmitis (0.3%), cataract (0.2-3.6%), and rhegmatogenous retinal detachment (RRD) (0.9%) [8-11]. Of critical importance in the injection process is to perform the injection at approximately 3.5 to 4 mm from the limbus, given that penetration at more than 4.5 mm from the limbus may damage the anterior base of the vitreous and ora serrata. Such trauma can cause severe damage to all layers of the retina, including retinal tears or holes, that can progress to vision-threatening conditions such as vitreous hemorrhage, RRD, and choroidal detachment [12]. Although there have been reports on the incidence of RRD after intravitreal injection, to our knowledge, there have been no studies performed only in Korean patients. Furthermore, most studies that have included large numbers of participants have entailed the pooling of data from multiple centers with multiple physicians or are limited by a relatively small sample size of patients treated by a single physician [6]. In contrast, this study sought to report the incidence of RRD after intravitreal injections by a single physician in comparison with that reported previously and to describe the clinical features and outcomes in a large number of patients who received intravitreal injections from a single physician.

Materials and Methods

The study was approved by the Institutional Review Board of Yonsei University Gangnam Severance Hospital (IRB No. 3-2019-0283) and adhered to the tenets of the Declaration of Helsinki and the Good Clinical Practice guidelines. We retrospectively reviewed the medical records of patients who received intravitreal injections administered by a single retinal specialist (M. K.) between February 2012 and January 2019. Demographic data at baseline, including patient age and sex, and clinical data such as diagnoses, the number of intravitreal injections received, and the agent injected, were collected.

All patients provided written informed consent, which was documented electronically before each injection. The injection was administered in an operating room or a treatment room in the outpatient clinic. A topical dilating agent (0.5% tropicamide/0.5% phenylephrine, Tropherine®; Hanmi Pharm Co. Ltd., Seoul, Korea) was administered 30 minutes before injection. Additionally, topical 0.5% proparacaine hydrochloride (Alcaine®; Alcon, Fort Worth, TX, USA) was instilled in the eye before each injection, followed by application of a povidone-iodine swab to the eyelid, eyelashes, and lid margin. A sterile speculum was inserted, and 5% povidone-iodine solution was introduced over the ocular surface to sterilize the conjunctival sac. The intravitreal injection was performed at 3.5 to 4.0 mm from the limbus, mainly in the superotemporal or inferotemporal quadrant. A 30-gauge needle was used for all injections, except those involving Ozurdex® (Allergan Inc., Dublin, Ireland), for which an enclosed 22-gauge needle was used. All patients received topical 0.3% gatifloxacin (Gatiflo®; Handok, Seoul, Korea) for one week after each injection [6,7,13].

Patients were followed up at one month after each injection. All patients underwent a fundus examination including ultra-widefield scanning laser ophthalmoscopy (Optomap; Optos, Marlborough, MA, USA) and dilated binocular indirect ophthalmoscopy at each visit. Patients were provided with verbal and written instructions to visit the clinic earlier or to contact a local ophthalmologist if they developed sudden floaters, flashes, a visual field defect, loss of vision, eye pain, or redness. Patients presenting to our clinic with such symptoms were examined immediately. Patients with less than three months of follow-up data after treatment were excluded.

All fundus images, time of occurrence, features of the condition, and the course of treatment were reviewed if RRD developed after intravitreal injection. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 23.0; IBM Corp., Armonk, NY, USA).

Results

A total of 9,484 injections was performed in 1,739 eyes of 1,480 patients. The mean patient age at the time of the first injection was 59.7 ± 17.6 (range, 0-94) years, and 842 patients (56.9%) were male. The mean follow-up duration was 26.3 ± 19.3 (range, 3.0-82.0) months (Table 1). The average number of injections per eye was 5.3 ± 6.5 (range, 1-46). The agents injected were as follows: bevacizumab (Avastin®; Genentech Inc., San Francisco, CA, USA) in 5,766 (60.8%);

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aflibercept (Eylea®; Bayer, Leverkusen, Germany) in 1,603 (16.9%); ranibizumab (Lucentis®; Genentech Inc.) in 1,385 (14.6%); dexamethasone intravitreal implant (Ozurdex®; Allergan, Inc.) in 654 (6.9%); and others (including ganciclovir [Cymevene®; Hoffmann-La Roche, Welwyn Garden City, UK], steroids, antibiotics, and antifungals) in 76 (0.8%) (Table 1).

The most common condition requiring intravitreal injection was exudative AMD (n = 353, 23.9%), which was followed by vitreous hemorrhage associated with diabetic retinopathy (n = 286; 19.3%), retinal vein occlusion with macular edema (n = 221, 14.9%), diabetic macular edema (n = 169, 11.4%), central serous chorioretinopathy (n = 146, 9.9%), and uveitis (n = 89, 6.0%) (Table 2).

The occurrence of RRD was noted as a complication in only one eye from one patient, yielding incidence rates of 0.01% per injection and 0.06% per injected eye. This complication occurred in a 36-year-old man with a diagnosis of PDR accompanied by vitreous hemorrhage in his left eye who received three consecutive intravitreal injections of bevacizumab. He was scheduled to return for an outpatient follow-up visit at one month after the final injection but experienced sudden vision loss in the treated eye after only two weeks. Dilated fundus examination revealed a peripheral retinal tear at the superotemporal quadrant with bullous retinal detachment in the temporal half of the retina involving the macula (Fig. 1). The patient underwent prompt vitrectomy with gas tamponade. During subsequent postoperative follow-up, the patient remained stable without complications, such as recurrence of RRD, or need for additional injections or other treatment.

Table 1. Baseline characteristics of the study population

Characteristic	Value
Total number of injections performed	9,484
Total number of subjects/eyes	1,480/1,739
Age at time of first injection (years)	59.7 ± 17.6
Sex (male)	842 (56.9)
Injections performed	9,484 (100)
Bevacizumab	5,766 (60.8)
Aflibercept	1,603 (16.9)
Ranibizumab	1,385 (14.6)
Dexamethasone implant	654 (6.9)
Other (antibacterial, antiviral, or antifungal)	76 (0.8)
Follow-up duration (months)	26.3 ± 19.3

Values are presented as mean ± standard deviation or number (%).

Table 2. Diagnoses of patients treated with intravitreal injections

Diagnose	Value
Neovascular age-related macular degeneration	353 (23.9)
Proliferative diabetic retinopathy with vitreous hemorrhage	286 (19.3)
Retinal vein occlusion with macular edema	221 (14.9)
Diabetic macular edema	169 (11.4)
Central serous chorioretinopathy	146 (9.9)
Uveitis (including uveitic macular edema)	89 (6.0)
Retinopathy of prematurity	33 (2.2)
Cytomegalovirus retinitis	22 (1.5)
Hypertensive retinopathy	9 (0.6)
Retinal vasculitis	6 (0.4)
Other (including endophthalmitis and acute retinal necrosis)	146 (9.9)
Total	1,480

Values are presented as number (%).

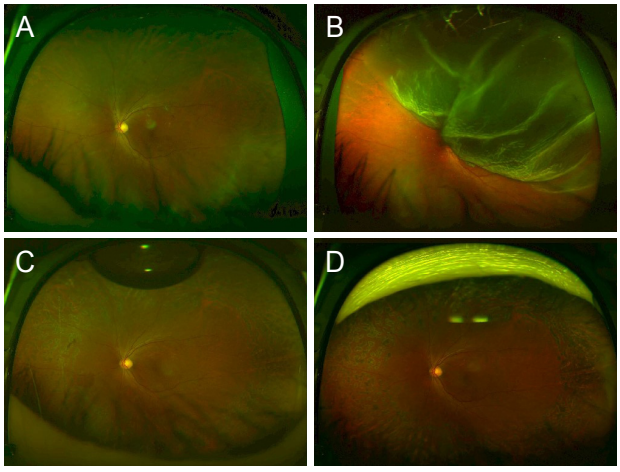

Figure 1. Retinal detachment after intravitreal injection of anti-vascular endothelial growth factor in a 36-year-old man diagnosed with proliferative diabetic retinopathy accompanied by vitreous hemorrhage in his left eye. (A) A wide-field fundus image acquired before intravitreal bevacizumab injection shows residual vitreous hemorrhage without peripheral retinal breaks. (B) Two weeks after intravitreal bevacizumab injection, a bullous retinal detachment was evident. (C) After prompt vitrectomy, a well-attached retina can be seen at one month postoperatively. (D) Follow-up imaging at 18 months after surgery revealed a stable flat retina with peripheral scarring from laser photocoagulation.

Discussion

In the present retrospective review of 9,484 intravitreal injections performed by a single retinal specialist, we identified only one case complicated by RRD among 1,739 eyes from 1,480 patients, for an incidence rate of 0.01% per injection. According to previous studies, the incidence of RRD after intravitreal injection varies from 0% to 0.9% [6,7,9,14-20]. The incidence in our study, which is based on a relatively large number of cases, was significantly lower than that in previous reports. This discrepancy may reflect differences in study design such as number of physicians involved, perioperative procedures, and the treating physician's proficiency and technique.

Park et al. [21] reported that 10.39 cases of RRD per 100,000 people in South Korea occurred from 2007 to 2011, which is an incidence of 0.01%. This rate is similar to that in our study, suggesting that intravitreal injection does not necessarily increase the risk of RRD compared to its incidence in the general population if appropriate perioperative management protocols and injection techniques are used. However, it is difficult to exclude the risk of retinal detachment after intravitreal injection, especially given that all intravitreal injections were administered by the same physician in our study and the variable incidence rates reported in previous research [6].

Adopting the correct injection technique is critical to minimizing the risk of serious complications. A crucial step in reducing the incidence of RRD may be identifying the correct anatomic location for injection. If the needle were to penetrate posterior to the appropriate site, the anterior base of the vitreous and ora serrata could be damaged, and the entire retina could be breached. Such damage can lead to retinal tears and progress to retinal detachment [22]. Therefore, to minimize the risk of RRD, physicians should avoid the anterior base of the vitreous and ora serrata by targeting the area 3.5 to 4.0 mm from the corneolimbal margin and, at the same time, should not point the tip of the needle too far posteriorly. Furthermore, to avoid complications such as vitreous incarceration, the sclera should be penetrated obliquely rather than perpendicularly. Indeed, there are reports that a double-plane tunnel technique can significantly lower the risk of RRD. Using this technique, the sclera is first penetrated at an angle of 15° to 30°, after which point, the needle is repositioned to an angle of 45° to 60° while the sclera is still engaged [22-24].

The RRD case in our study occurred in a male patient with myopia (-5.25 diopters) who was treated with three consecutive intravitreal bevacizumab injections prior to occurrence of RRD. A previous study by Meyer et al. [7] reported a higher incidence of RRD in myopic eyes, with four of the five RRD cases having myopia ranging from -1.75 to -5.5 diopters. The authors recommended examining myopic eyes for lattice degeneration, atrophic holes, or vitreous tractions with a contact lens and treating these lesions prior to proceeding with a patient's first injection. Although no definite retinal tear or lattice degeneration was found prior to injection in our case, a careful fundus examination including a contact lens exam may help to prevent post-injection RRD in myopic eyes. Furthermore, the indication for treatment in this particular patient was PDR. The natural course of PDR is a cycle of proliferation and regression of new vessels, proliferation of fibrous tissue, adhesion between the posterior vitreous surface and fibrovascular proliferations, and contraction of the posterior vitreous. Intravitreous injection of bevacizumab could perhaps worsen this natural course by stimulating regression of the vascular component of fibrovascular proliferation with a concurrent increase in fibrosis, eventually aggravating the retinal traction [25]. As this so-called "crunch syndrome" is a well-known contributing factor to tractional retinal detachment, injections should be performed only after careful deliberation in patients with PDR.

Our study population included diseases like acute retinal necrosis and cytomegalovirus retinitis that tend to pair with a high incidence of retinal tear. In these conditions, a hole or tear can form in the necrotic area due to disease progression regardless of intravitreal injection. However, in our study, there was no patient who presented with retinal tear or retinal hole. The small number of patients with these diseases seems to have influenced the results.

Our study has several limitations. First, all the patients enrolled were from the practice of one retinal specialist at a single tertiary hospital. Second, there was only one confirmed case of RRD as a complication, which made it difficult to determine whether or not the risk of RRD depends on injection site, agent injected, or another factor such as the disease being treated. Therefore, further research to answer these questions is needed in the future. However, the strength of our study is that it is a single-center, single-practitioner case

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series with a relatively long follow-up period that included a larger number of patients than in previous studies, which allowed us to minimize the variations introduced by multiple practitioners.

The incidence of RRD after intravitreal injection in our study was similar to that reported in previous studies and to the overall incidence of RRD in the Korean population. This finding suggests that intravitreal injection is a safe treatment modality when performed with a proper technique and safety precautions.

Conflicts of Interest

The authors have no conflicts to disclose.

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