Incidence of Post-Intravitreal Anti-VEGF Endophthalmitis at Thammasat University Hospital

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Background: *Anti-vascular endothelial growth factor (anti-VEGF) drugs have been used as ophthalmic injections to treat various eye diseases. Recently, the use of this drug has gradually increased as awareness of potential complications, especially the occurrence of endophthalmitis.*
Objective: *To report the incidence rate, clinical features, management, and presumed risk factors of acute post-intravitreal anti-VEGF drug injection endophthalmitis secondary to therapeutic intravitreal ranibizumab and bevacizumab injections.*
Material and Method: *A retrospective review of all consecutive eyes after intravitreal injections was performed at Thammasat University Hospital, Pathumthani, from June 2008 to September 2013. Data collected at diagnosis included patient demographics, intravitreal injection details, pre- and post-injection management, visual acuity, clinical features and managements, causative organisms, and clinical outcomes.*
Results: *During the 5-year-study interval, 1,169 intravitreal injections were performed. The overall incidence rate of endophthalmitis was 0.17% (2 of 1,169 injections). In our series, the endophthalmitis occurred after the 1st and 2nd injection. Bacterial cultures and gram stain revealed coagulase-negative Staphylococcus species (n = 1) and no organism found (n = 1). All cases were treated efficiently in limiting the devastating sequels by intravitreal antibiotics, steroids and pars plana vitrectomy. The result showed that recovery of useful vision was found in one case and devastating vision in another case.*
Conclusion: *Acute endophthalmitis is a rare potential complication after intravitreal injection. Prognosis of endophthalmitis varies widely depending upon the severity of the infection, the organism involved and the amount of damage the eye sustains from inflammation and scarring. Further studies are required to clarify the best prophylactic techniques to prevent this rare complication.*

Keywords: *Endophthalmitis, Anti-VEGF drug, Intravitreal injection, Ranibizumab, Bevacizumab*

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Bevacizumab and ranibizumab are anti-vascular endothelial growth factor (anti-VEGF) drugs that have effects in new vessel regeneration elimination, inflammatory reduction and macular edema reduction[1]. They have thus been used in ophthalmic injections to treat various eye diseases such as age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusion (RVO) and retinopathy of prematurity (ROP)[2-5].

Recently, the use of bevacizumab and ranibizumab has gradually increased as awareness of potential complications, especially as the occurrence of endophthalmitis has risen[6]. There were reports on an international level on endophthalmitis that range from 0.019% to 0.54% intravitreal injections performed[7-9] and that bacterial infection was the most common infection with a belief that bacteria was inhibited around the ocular surface[10]. Nonetheless, non-sterile devices or drugs should be avoided to prevent infections. Several studies have indicated that coagulase-negative *Staphylococcus* was the most common microbe found during infections[6]. At present, there are no standard conclusive recommendations on infection prevention[11]. Thus, antibiotics have been widely prescribed during pre- and post-injections. The present study reports the incidence rate, clinical features, managements, and presumed risk factors of endophthalmitis following intravitreal injection occurred in Thammasat University Hospital.

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Material and Method

The Human Research Ethics Committee of Thammasat University (No. 1 Faculty of Medicine) approved this retrospective cohort study conducted by reviewing medical records of patients who underwent bevacizumab and ranibizumab intravitreal injections performed by four retina specialists and ophthalmology

residents at Thammasat University Hospital, Pathumthani, from June 1, 2008 to September 30, 2013. Data collected at diagnosis included patient demographics such as sex and age, intravitreal injection details, the number of injections, and complications related to the patients with endophthalmitis.

Intravitreal injections practiced at Thammasat University Hospital was the standard procedure to prevent infections that is to inject in a clean room, wear sterile gloves, wear a mask, wear surgery cap, place local anesthetic drops and clean patient's eyes using povidone-iodine. A sterile surgical drape that covered patient's nose and mouth and a sterile lid speculum were used before performing injections. The lid speculum and drape were removed, and the periorbital region was gently cleaned using a sterile saline solution. After injections, antibiotic eye drops were prescribed and patients advised to avoid getting water in the eyes for about 7 days. Vitreoretinal specialists confirmed the diagnosis of presumed microbial endophthalmitis in all cases by using clinical symptoms that called for agar vitreous culture for bacteria and fungus in all patients suspected of intraocular endophthalmitis. The decision to use systemic antibiotics or to perform a vitrectomy was the decision of the managing vitreoretinal ophthalmologists.

The purpose of the study was to determine eye infection rates after intravitreal injection of anti-VEGF drug. The study also explored treatments given to patients and vision measurements after infections were treated.

Results

There were 933 injections with bevacizumab in total as there were 236 ranibizumab eye injections. The total number was 1,169 injections, for 519 eyes, with intravitreal injections of 2.25 times per eye. The minimum number of eye injections was one time and the maximum six times per eye. Endophthalmitis was found only in one case in the bevacizumab group (0.107%; 1/933) and one case in the ranibizumab group (0.423%; 1/236). The characteristics in each patient are as follows.

Case 1

A 52-year-old female patient diagnosed with diabetic macular edema visited the clinic with eye pain, eye irritation, and watering eyes. The patient had been given intravitreal bevacizumab injections 4 days earlier, which was the second injection performed, one month apart from the first injection. On the injection day, the injection was performed in an operating room that had been used to perform an injection for patient with corneal infection. However, the room was cleaned with standard protocol prior to the injection. The patient was given anesthetic drops (0.5% tetracaine hydrochloride) and her eyes were flushed with 5% povidone-iodine. The patient was injected through pars plana area from superior temporal quadrant, 4 mm away from limbus. Antibiotics drops were placed after the injection along with antibiotics eye drop prescribed for continuous use for 1 week. The patient had no history of getting water in her eyes for 72 hours after the injection. The patient later experienced eye pain, eye redness, and discharge. Her vision also dropped.

The physical examination showed best corrected visual acuity (BCVA) at 20/100. Inflammation of aqueous and vitreous humor was detected. The patient was treated by intravitreal injection of 1 mg/0.1 ml vancomycin, and 2.25 mg/0.1 ml ceftazidime and vitreous tapping immediately. Vitreous culture showed coagulase-negative *Staphylococcus*. The patient received topical vancomycin and ceftazidime every hour as well as intravenous vancomycin and ceftazidime. Three days later, the vision had further decreased to counting fingers, and there was increased intraocular inflammation so the patient underwent pars plana vitrectomy (PPV), and received intravitreal 1 mg/0.1 ml vancomycin as well as 2.25 mg/0.1 ml ceftazidime injection. Throughout the treatment period, 1% methylprednisolone eye drops were given for about five days after PPV to reduce inflammation. One month after presentation, the patient's vision had improve to 5/200 and mild anterior chamber reaction and minimally vitreous clumping. The medication was continued. Her 3-month follow-up visit showed BCVA improved to 20/200 and no anterior chamber cells with mild epiretinal membrane.

Case 2

A 62-year-old male was given 1st bevacizumab injection for proliferative diabetic retinopathy with vitreous hemorrhage through pars plana area from superior temporal quadrant, 3.5 mm away from limbus. After the injection, antibiotics drops were given. Unfortunately, the patient did not use antibiotic eye drops prescribed later on. The patient had no history of getting water in his eyes for 72-hour post-injection though he had eye pain, eye redness, and reduced vision to hand movement and later was diagnosed with endophthalmitis.

The patient was then treated with intravitreal 1 mg/0.1 ml vancomycin, and 2.25 mg/0.1 ml ceftazidime injections. His vitreous fluid was also tapped for culture. Vitreous cultures were negative. Later, his clinical signs worsened. His vision dropped to light projection and intraocular inflammation got worse. The detail of retina cannot be seen because of inflammation and vitreous hemorrhage for diabetic retinopathy. Pars plana vitrectomy with intravitreal vancomycin and ceftazidime injection was performed to clear the inflammation and hemorrhage. The patient was maintained on the systemic and topical vancomycin, ceftazidime and anti-inflammatory therapy. One-week post-operation, his symptoms improved. The patient's vision had improved back to 5/200. Antibiotic was then change to topical levofloxacin and oral Ciprofloxacin.

Discussion

The improved drug efficacy and specific indication for intravitreal injection led to a dramatic increase in intravitreal injections, especially anti-VEGF injections. Endophthalmitis is a complication of intravitreal injections that is rare, but has severely poor prognosis. Intravitreal injection technique was firstly practiced around 1980s to treat viral eye infections, for example, ganciclovir was use in patients with cytomegalovirus (CMV) eye infection in AIDS patients[12]. Post-injection infection rate was approximately 0.1% per injection[4,6,13-16].

Ten years later, in the 1990's, intravitreal steroids injections were introduced to treat age-related macular degeneration, diabetic macular edema and retinal vein occlusion. Rate of the post-intravitreal injection reported approximately 0.019% to 0.54% infection per injection[6,7]. The early 2000's was the beginning of anti-VEGF injections to treat neovascular AMD. VEGF Inhibition Study in Ocular Neovascularisation (VISION) trial[17] was conducted to study pegatanib, a selective VEGF antagonist. The study result indicated that the incidence of endophthalmitis was about 0.06% per injection. There were also two landmark studies of ranibizumab for neovascular AMD treatment[4,16]. Both studies showed the incidence of post-injection endophthalmitis of 0.05% per injection. At the time, the United States Food and Drug Administration had not yet approved bevacizumab but the drug was already widely used off-label. There was another study on wet AMD in a Pan-American Collaborative Retina Study (PACORES) that found an infection rate of approximately 0.16%[18]. This study conducted at Thammasat University Hospital found that the overall incidence rate of post intravitreal injection endophthalmitis was 0.17%, which was similar to international reports.

As with all intraocular surgeries, the source of bacteria in endophthalmitis is the normal flora inoculated on the ocular surface and adnexa such as lid, lash and conjunctiva. Several studies involving intraocular surgeries reviewed those coagulase-negative staphylococci bacteria was the most common pathogen[19]. Endophthalmitis vitrectomy study (EVS) found that 94% of culture-positive endophthalmitis caused by gram-positive bacteria and that 70% were coagulase-negative staphylococci, 10% were *Staphylococcus aureus*, 9.0% were *Streptococcus* species, 2% were *Enterococcus* species, and 3% were gram-positive. Other gram-negative species were about 6%. However, meta-analysis studies found streptococcal at nearly 30% of intravitreal injections, 3-4 times higher than other intraocular surgeries. The possible cause was the infection of normal flora in the mouth from droplet aerosol[10].

Eye clinic at Thammasat University Hospital have common practice in intravitreal injections that the injections can be performed in either an office setting or operating room where injectors wear masks and surgery caps, and that anesthetics are applied prior to injections along with 5% povidone-iodine solution used to clean the patients' eyes prior to every injection. Clean sheets, sterile eye speculum, and post-injection antibiotic are applied. It is recommended that patients avoid getting water in their eyes for 7 days after injections.

It should also be noted that, in the first case, coagulase-negative staphylococci was found. The physicians are masked and the patient is draped, it can prevent oropharyngeal organisms that found commonly caused endophthalmitis after intravitreal injection but for this case, the patient received injections after another patient with corneal infection had been in operation room. It may have been a risk factor for endophthalmitis; in addition the second patient (case II) did not continuously apply post-injection antibiotic eye drops. From the survey of intravitreal injection techniques among retinal specialists in the United States, a majority of retinal specialists (81%; 608/753) use prophylactic topical antibiotics post-injection[20]. However, there are many reports using post-injection topical antibiotic drops does not reduce the risk of endophthalmitis[11,21]. In patients having endophthalmitis, the infections were found after 1.5 needles from 2.5 needles per eye

on average with minimum of one and maximum of six times per eye. This indicates that the incidence of infection does not depend on the number of intravitreal injections.

Limitations of the present study are that it is retrospective and, for that fact is an uncontrolled non-comparative case series. Anyhow, this study reviewed 1,169 anti-VEGF intravitreal injections performed at Thammasat University Hospital for the period of about five years that should well represent the incidence of post-injection endophthalmitis in a tertiary hospital. The number of endophthalmitis after intravitreal injection is quite small so it is difficult to draw conclusions about risk factors or proper management from such a small sample.

Conclusion

The present study shows that the incidence of infection is low at about 0.17%, which coincided with international studies. Prognosis of endophthalmitis varies widely depending upon the severity of the infection, the organism involved and the amount of damage the eye sustains from inflammation and scarring. The further study should address the management of post-injection endophthalmitis and the best prophylactic techniques to prevent this rare complication.

What is already known on this topic?

Intravitreal injections of anti-VEGF drugs such as ranibizumab and bevacizumab have become standard care to treat various eye diseases. Recently, the use of this drug has gradually increased with awareness of potential complications, especially the occurrence of endophthalmitis. There were reports in an international level on endophthalmitis that range from 0.019% to 0.54% of intravitreal injections performed. But post intravitreal injection endophthalmitis appeared to be associated with more virulent organisms than in intraocular surgery. This study reports the incidence, clinical features, management, and presumed risk factors of endophthalmitis following intravitreal injection occurred in Thammasat University Hospital.

What this study adds?

This study shows that the incidence of infection is low at about 0.17%, which coincided with international studies. The patients need prompt diagnosis and early management to prevent further complications. Prognosis of endophthalmitis varies widely depending upon the severity of the infection, the organism involved and the amount of damage the eye sustains from inflammation and scarring.

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Potential conflicts of interest

None.

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อุบัติการณ์การเกิดการติดเชื้อหลังการฉีดยาในกลุ่ม anti-VEGF เข้าน้ำวุ้นนัยน์ตาในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

ณวพล กาญจนารัณย์, ดวงมนตรี โรจน์ดำรงรัตนา, ประธาน ปิยสุนทร

ภูมิหลัง: *ยากลุ่ม anti-vascular endothelial growth factor (anti-VEGF) ได้ถูกนำมาใช้โดยการฉีดเข้านัยน์ตาเพื่อรักษาโรคตาหลายชนิด พบว่าปัจจุบันมีการใช้ยากลุ่มนี้มากขึ้นเรื่อย ๆ ทำให้มีการตระหนักถึงข้อแทรกซ้อนที่อาจจะเกิดขึ้นได้ โดยเฉพาะอย่างยิ่งการเกิดการติดเชื้อที่ตา*

วัตถุประสงค์: *เพื่อรายงานอุบัติการณ์ รวมถึงลักษณะทางคลินิก การรักษา และปัจจัยเสี่ยงของการติดเชื้อนัยน์ตา อันเกี่ยวเนื่องกับการได้รับการรักษาด้วยยากลุ่ม anti-VEGF ตามหลังการฉีดยา ranibizumab และ bevacizumab เข้าน้ำวุ้นนัยน์ตา*

วัสดุและวิธีการ: *เป็นการศึกษาเวชระเบียนย้อนหลังของทุกตาที่ได้รับการฉีดยาเข้าน้ำวุ้นนัยน์ตาในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ จังหวัดปทุมธานี ตั้งแต่เดือนมิถุนายน พ.ศ. 2551 จนถึง กันยายน พ.ศ. 2556 โดยเก็บรวบรวมข้อมูลที่ได้รับวินิจฉัยโรค ลักษณะประชากร รายละเอียดวิธีการฉีดยาเข้าน้ำวุ้นนัยน์ตา การดูแลก่อนและหลังการฉีดยา ค่าสายตา ลักษณะทางคลินิกและการรักษาตลอดจนเชื้อที่เป็นสาเหตุ และผลการรักษา*

ผลการศึกษา: *พบว่าระหว่างช่วงระยะเวลาการศึกษา 5 ปี มีการฉีดยาเข้าน้ำวุ้นนัยน์ตาทั้งสิ้นจำนวน 1,169 ครั้ง พบอุบัติการณ์การเกิดการติดเชื้อนัยน์ตา 0.17% (จำนวน 2 ใน 1,169 ครั้ง) โดยพบการติดเชื้อภายหลังการฉีดยาครั้งที่ 1 และการฉีดยาครั้งที่ 2 การเพาะเชื้อแบคทีเรียและการย้อมสีกรัมพบเชื้อ Staphylococcus species ในผู้ป่วยหนึ่งราย และไม่พบเชื้ออีกหนึ่งราย ผู้ป่วยทุกรายได้รับการรักษาโดยการฉีดยาปฏิชีวนะเข้าน้ำวุ้นนัยน์ตา ยาสเตียรอยด์ และการทำผ่าตัด pars plana vitrectomy การมองเห็นกลับมาใช้การได้ในผู้ป่วยหนึ่งราย และมีการมองเห็นแย่ในผู้ป่วยอีกหนึ่งราย*

สรุป: *การติดเชื้อที่ลูกตาเป็นข้อแทรกซ้อนที่พบได้น้อยภายหลังการฉีดยาเข้าน้ำวุ้นนัยน์ตา โดยการพยากรณ์โรคมีความแตกต่างกันขึ้นอยู่กับความรุนแรงของการติดเชื้อ เชื้อที่ตรวจพบความเสียหายจากการอักเสบและแผลเป็นที่เกิดขึ้นต่อเนื่องมา การศึกษาเพิ่มเติมในอนาคตที่เกี่ยวกับการป้องกันการติดเชื้อในน้ำวุ้นนัยน์ตามีความจำเป็นเพื่อป้องกันภาวะแทรกซ้อนที่จะเกิดขึ้นตามมา*