

# Incidence of endophthalmitis after intravitreal application of anti VEGF therapy at the University Clinical Center in Tuzla, Bosnia and Herzegovina

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## ABSTRACT

**Aim** To report the incidence of endophthalmitis following the use of intravitreal injection of anti-vascular endothelial growth factor (anti VEGF) therapy.

**Methods** In this retrospective study a total of 986 intravitreal bevacizumab injections were applied between January 2008 and April 2015 at the University Clinical Center Tuzla, Bosnia and Herzegovina (B&H). Since January 2012, a total of 55 intravitreal ranibizumab injections were applied and since October 2014, 60 intravitreal aflibercept injections were applied to patients.

**Results** Two cases of endophthalmitis following intravitreal injection of bevacizumab occurred and none after ranibizumab or aflibercept. The overall incidence of clinical endophthalmitis was 0.2%.

**Conclusion** The results suggest that a low rate of endophthalmitis can be achieved by means of a protocol. This is a very important study as it is the first of this kind in B&H that documents the incidence of endophthalmitis after intravitreal application. Currently, bevacizumab in B&H is most frequently used intravitreal anti-vascular endothelial growth factor due to very low price.

**Key words:** bevacizumab, aflibercept, ranibizumab, complications of intravitreal application

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## INTRODUCTION

Endophthalmitis is uncommon, but very severe ocular inflammatory process that can lead to blindness (1). During this process, inflammation affects vitreous cavity along with the retinal and uveal components of the eye. After eye surgery or intravitreal application of anti vascular endothelial growth factor (anti VEGF) post-operative endophthalmitis is possible to occur, and it can have two forms, either sterile or infectious (2). Since its beginning in 2004, intravitreal injections of anti VEGF in whole world have had a huge impact on treatment of variety of ocular conditions (3). The number of intravitreal injections is increasing in Bosnia and Herzegovina (B&H). Currently, at the University Clinic Center (UCC) in Tuzla, B&H, intravitreal injections have become a common route of administration of medications. At UCC Tuzla currently we are applying intravitreal injections bevacizumab, ranibizumab and aflibercept. This intravitreal injections are applied for a variety of conditions including complications of diabetic retinopathy, such as diabetic macular edema (DME) and as well other retinal-vascular disorders, such as branch retinal vein occlusion, central retinal vein occlusion and as well age related macular degeneration (AMD) (4-6). At this moment only ranibizumab and aflibercept are labeled for intravitreal use, while bevacizumab is currently also being used "off-label" for the treatment of ocular disease. This off-label intravitreal injections of bevacizumab have been given for the treatment of neovascular and exudative ocular diseases since May 2005 (7). To our knowledge until today, from February 2004 bevacizumab has been approved by the US Food and Drug Administration (FDA) for treating patients with metastatic colorectal cancer (8). All over the world between 1997 and 2001, fewer than 5,000 intravitreal injections were performed annually, while more than 800,000 were performed in 2007 (9).

To minimize any complication or infections after intravitreal application of anti VEGF several protocols have been proposed (10-11). Recent surveys have suggested that 40% of retina specialists use topical antibiotics before anti-vascular endothelial growth factor intravitreal injections, and 86% use topical antibiotics after anti-vascular endothelial growth factor intravitreal injections (12).

The aim of this study was to investigate the incidence of endophthalmitis following the use of intravitreal injection of anti-vascular endothelial growth factor (anti VEGF) therapy.

## PATIENTS AND METHODS

University Clinic Center of Tuzla is a single health institution equipped for the intravitreal application of anti VEGF therapy in north-eastern part of B&H. This is a single-center retrospective analysis of all intravitreal application at the UCC Tuzla. All patients who received intravitreal injections of bevacizumab, ranibizumab and aflibercept were included in this study. Patients receiving other intravitreal injections (including corticosteroids or antibiotics) were excluded. The indications for intravitreal injection included exudative age-related macular degeneration (AMD), choroidal neovascular membranes secondary to myopic degeneration, cystoid or diffuse macular edema from central and branch vein occlusions, and as well edema due to a diabetic complication. All intravitreal injections were recorded in doctor and nursing logbooks. In this study provisions of the Helsinki Declaration were followed.

Before application all the patients who were treated with 0.05 ml injection containing 1.25 mg of bevacizumab, 0.3 mg /0.05 mL ranibizumab or 2.0 mg/0.05 mL aflibercept, underwent complete eye examination. The complete eye examination included determination of best-corrected visual acuity, slit-lamp examination, intraocular pressure measurement and retinal thickness measurement by optical coherence tomography. After written informed consents were obtained, all patients were treated. The informed consent was given to all patients due the risks of intravitreal injection which included pain, bleeding, retinal detachment, cataract, increased transient IOP, infections and sterile endophthalmitis. Injections were performed by retinal specialist in the operation room. The medications were given under aseptic conditions. Lids and conjunctiva were prepared with 5% povidone iodine, followed by the placement of an eyelid speculum. Intravitreal injections were injected with a needle in infero-temporal quadrant through pars plana (3,5 – 4,0 mm from limbus) into the vitreous cavity. Patients were instructed to administer topical Maxitrol (Alcon) 3 times daily for 5 days. All applications were performed as an outpatient pro-

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cedure. Patients were told to return to the hospital immediately if visual disturbance, pain, or redness of the eyes were noticed. Generally all the patients following intravitreal injections were followed up in the clinic usually at 1-3 monthly intervals.

Clinical diagnosis of endophthalmitis was made on the basis of presence of anterior chamber reaction, keratic precipitates, hypopyon, fibrin and/or posterior synechia. Ultrasound examination was performed with (10MHz transducer, UltraScan, ALCON Inc, Fort Worth, TX, USA).

## RESULTS

In a period of 7 years a total of 986 patients with intravitreal bevacizumab injection, 1.25 mg/0.05 mL was treated. Since 2012 fifty-five patients had been treated with intravitreal ranibizumab injection 0.3 mg /0.05 mL and since October 2014 sixty patients had been treated with intravitreal aflibercept injection 2.0 mg/0.05 (Table1).

**Table 1. Total number of intravitreal injections of anti VEGF at UCC Tuzla and the number of endophthalmitis cases that occurred after intravitreal injection**

Type of anti VEGF	Total number of intravitreal injections	Number of endophthalmitis cases after intravitreal injections
RANIBIZUMAB	55	0
BEVACIZUMAB	986	2
AFLIBERCEPT	60	0

The overall incidence of clinical endophthalmitis was 0.2%. Injections were administered in an operating room. Patients presented with decreased vision, pain and red eye. Two cases of endophthalmitis following intravitreal injection of bevacizumab occurred and none after ranibizumab or aflibercept. Both patients with endophthalmitis were males. The mean interval between intravitreal injections and onset of symptoms was 3 days.

## DISCUSSION

The results suggest that a low rate of endophthalmitis can be achieved by means of a protocol that includes the use of topical povidone-iodine, a

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sterile lid speculum, and topical anesthetic and postoperative application of topical antibiotics for seven days. It should be emphasized that this is the first study in B&H that documents the incidence of endophthalmitis after intravitreal application. It is known that bevacizumab in B&H is the most frequently used intravitreal anti-vascular endothelial growth factor due to very low price. In the last few months many efforts have been made to include ranibizumab and aflibercept to hospital list. A review of literature identified a number of reports of endophthalmitis rates after large series of intravitreal injections. The frequency of endophthalmitis after intravitreal anti VEGF reported in available scientific literature varies from 0.01% to 1.6% (13-18).

We expect that with the increasing number of applications of anti VEGF, the overall number of endophthalmitis will increase as well in B&H in the near future. Despite the growing number of indications and agents for intravitreal injections, there is no consensus on peri-injection guidelines for the prophylaxis of endophthalmitis (19). Although endophthalmitis cannot be prevented in all cases, certain strategies must be proposed on the global level. In conclusion, endophthalmitis remains very a severe complication of intravitreal application of anti VEGF but infrequent.

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## TRANSPARENCY DECLARATIONS

Competing interest: none to declare.

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## Incidenca endoftalmitisa nakon intravitrealne primjene anti-VEGF terapije na Univerzitetsko kliničkom centru Tuzla

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### SAŽETAK

**Cilj** Utvrditi incidencu endoftalmitisa nakon intravitrealne aplikacije antivaskularnog endotelno faktora rasta (anti-VEGF) na Univerzitetsko kliničkom centru u Tuzli.

**Metode** U ovoj retrospektivnoj studiji ukupno 986 intravitrealnih aplikacija bevacizumaba aplicirano je u periodu od januara 2008. do aprila 2015. godine na Univerzitetsko kliničkom centru u Tuzli (UKC Tuzla). Od januara 2012. godine ukupno je aplicirano 55 ranibizumaba dok je od oktobra 2014. broj apliciranih aflibercepta iznosio 60.

**Rezultati** Tokom ovog perioda desila su se dva slučaja endoftalmitisa nakon aplikacije bevacizumaba, a nije se desio ni jedan slučaj nakon aplikacije ranibizumaba ili aflibercepta. Incidenca endoftalmitisa iznosila je 0,2%.

**Zaključak** Rezultati indiciraju da se uz određene protokole može smanjiti incidenca endoftalmitisa. Ova studija je od velikog značaja jer se radi o prvoj studiji ovog tipa u Bosni i Hercegovini (BiH). Studijom su analizirani svi slučajevi endoftalmitisa nakon intravitrealne aplikacije anti-VEGF terapije. U BiH je bevacizumab najčešće korišten anti-VEGF zbog niske cijene.

**Ključne riječi:** bevacizumab, aflibercept, ranibizumab, komplikacije nakon intravitrealne aplikacije