Characteristics in patients with neovascular age-related macular degeneration developing postinjection endophthalmitis

Version 1

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Abstract

**Introduction:** Endophthalmitis after intravitreal injections is a rare but serious complication, which can lead to blindness. Strategies to minimise risk of complication is therefore of importance.

**Aim:** To investigate if the total number of intravitreal injections affects the risk of developing endophthalmitis. To identify other potential patient-related risk factors such as age, sex, eye affected, lens status, previous eye surgery, and type of drug used. Furthermore, to report the yearly incidence during the time period, specific characteristics of isolates of bacteria and clinical outcomes after the infection.

**Materials and methods:** A case series and retrospective case-control study. All patients with neovascular AMD admitted between January 2011 and August 2015 developing endophthalmitis following anti-VEGF injections from a total of five departments of ophthalmology were included. A randomly selected control group was recruited from patients receiving anti-VEGF-injections due to neovascular AMD without the complication.

**Results:** Thirteen cases of postinjection endophthalmitis were identified. An increased incidence of endophthalmitis was seen in our region. The total number of injections did not seem to affect risk of endophthalmitis; neither did any of the other studied patient-related characteristics show any significant differences. A tendency towards higher risk among females was shown (p=0.052). The average time between last received injection to symptom presentation was 3.3 days (range 0-8); 5.2 days (range 1-9) between injection and diagnosis. Positive microbial culture results were found in all eyes. Culture showed 61.5% *S. aureus*, 30.8% *S. epidermidis*, and 7.7% *S. pneumoniae*.

**Conclusions:** Our analysis could not identify specific patient-related characteristics correlating to the increased number of endophthalmitis cases. There was however a tendency towards females being at higher risk of infection. *Staphylococcus aureus* was more common in this study than in previous studies. Further investigation is warranted to identify sources of error and other potential risk factors for the complication.
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Abbreviations

AMD: Age-related macular degeneration
Anti-VEGF: Anti-vascular endothelial growth factor
CNS: Coagulase-negative staphylococci, such as *Staphylococcus epidermidis*. 
1. Introduction

1.1 Background

During the last few years a perceived increase of endophthalmitis has been noted within the patient group with neovascular age-related macular degeneration receiving intravitreal injections, at the Department of Ophthalmology, Örebro University Hospital. The purpose of this study was to identify common characteristics and evaluate if specific selected factors could appear as a risk of developing postinjection endophthalmitis in the above-mentioned endophthalmitis patient group.

1.2 Present knowledge

Endophthalmitis is a serious complication of invasive ocular procedures, which can lead to blindness. Prevention of the complication is essential to protect the vision [1]. Most patients will have worsened visual outcome even after treatment and an increased risk of future subsequent complications such as vitreous opacities, retinal detachment, and glaucoma [2].

During the last decade, the number of intravitreal injections primarily with anti-vascular endothelial growth factor (VEGF) agents has increased considerably [3]. A subsequent increase in serious ocular adverse events has also been noted, including endophthalmitis, although remaining at an infrequent rate [4]. Anti-VEGF injections are principally used for treatment of neovascular age-related macular degeneration (AMD), also known as exudative or wet AMD [5]. Additionally, anti-VEGF agents are also used in therapies of diabetic macular oedema [6], retinal vein occlusion [7], and neovascular glaucoma [8].

AMD is one of the leading causes of severe visual impairment and functional blindness among the elderly populations in developed countries [9] and is estimated to afflict 8.7 % of the world population [10]. Neovascular AMD accounts for 10% of all patients with AMD, constituting around 80 % of the most severely visually impaired in the group. Therapy with intravitreal anti-VEGF-injections can be performed repeatedly in earlier disease stages. The most commonly used agents are aflibercept, ranibizumab, and bevacizumab [5].
Purulent endophthalmitis as an exogenous infection can occur as a complication following ocular surgery, trauma, or intravitreal injections [11]. As a postinjection complication endophthalmitis is reported with a per-injection rate of 0.021-0.32% [2,12-17]. Symptomatic presentation of the complication such as pain in the eye and affected vision has been reported to occur at a mean of 2-4 days in different studies [14,18,19].

Although the characteristics of the complication are well documented, uncertainties of the best preventive strategies persist. Routines of the injection procedure vary widely in ophthalmological clinics around the world and no set standard exist on how the procedure should be performed [4]. Treatment of acute endophthalmitis is performed by an acute surgical intervention and is, if possible, conducted immediately after diagnosis [20].

Sterile endophthalmitis is less frequent than bacterial endophthalmitis and is more frequently reported when intravitreal bevacizumab is used [12,21]. Generally, sterile inflammation is followed by better visual prognosis and has different treatment strategies. Because of difficulties to distinguish it from bacterial infection clinically, many studies recommend treating it as bacterial endophthalmitis in any case due to risks of serious events following the complication [19,22,23].

In previous studies, mainly associated risk factors following cataract surgery have been analysed. In these studies associated patient-related risk factors include age above 85 years, male gender [24], diabetes mellitus, vulnerable immune system, trauma and postoperative eye rubbing [25]. In studies with postinjectional cause of endophthalmitis, possible risk factors are reported as diabetes mellitus, high age [12], blepharitis [2,12], eyelid movement during injection procedure, topical antibiotics administration failure before or after injection, subconjunctival anaesthesia [2], as well as the use of compounded medication such as bevacizumab [26]. Causative streptococcal species are reported to be more frequent in postinjectional endophthalmitis than in intraocular surgery [27], suggested to derive from oropharyngeal flora [16]. Most causative bacteria species vary between studies, although larger studies report coagulase-negative staphylococci (CNS) as the most frequent causative organism in patients developing endophthalmitis after intravitreal injections [2,16,28].
1.3 Aim and purpose

The purpose of this project was to investigate:

(1) Whether the total number of intravitreal injections with anti-VEGF agents due to neovascular AMD affects the risk of developing endophthalmitis, as a primary variable.

(2) To identify potential risk factors from characteristics and features such as age, sex, eye affected, lens status and previous eye surgery, type of drug used as secondary variables in the patients developing endophthalmitis.

(3) To report the yearly incidence of endophthalmitis treated after intravitreal injections during the time period, specific characteristics of isolates of bacteria and clinical outcomes after the injection-related complication.
2. Material and methods

2.1 Endophthalmitis and control groups

This report is a case series and retrospective case-control study. All cases of diagnosed endophthalmitis registered and treated between January 2011 and August 2015 at Örebro University Hospital were collected. The inclusion criteria concluded postinjection endophthalmitis following anti-VEGF therapy, with neovascular AMD as the treatment indication. Thirteen cases of infection were identified and data was collected from medical records. Twelve of the patients were referred from four other hospitals. All five ophthalmological departments (Dept.) were de-identified and randomly given letters as names, e.g. Dept. A, B, C, D, and E.

A control group consisting of 56 consecutively included non-endophthalmitis eyes of 51 neovascular AMD patients receiving anti-VEGF treatment, retrieved from the first half of the month of August 2015, was compared to the endophthalmitis case group.

Defined selected data was extracted from the medical records of each patient and arranged in tables for calculation and statistical analysis. All patient data was de-identified in the process.

2.2 Variables and Definitions

Baseline characteristics in both groups included age, total number of anti-VEGF intravitreal injections, sex, eye affected, lens status, and previous eye surgery. Total number of injections and Age were recorded at the time of endophthalmitis for the case group. Total number of injections was recorded as the number of injection on the date of inclusion for the control group. Sex was defined as either female or male. Eye affected implicated right or left eye. Lens status was divided into groups of phakic eyes, pseudophakic eyes or aphakic eyes. Previous eye surgery was grouped into answers of yes or no, where yes means previous intraocular surgery excluding cataract surgery, and no implies no previous intraocular surgery. Additional variables in the endophthalmitis group included type of anti-VEGF agent, average of days between last injection and presentation of endophthalmitis (symptoms of pain and decreased vision), average days between last injection and diagnosis. Microbial culture results were recorded, including type of bacteria and antibiotic susceptibility pattern.
2.3 Secondary control group

The national Swedish Macula Register was used to control the accuracy of the control group by comparing distribution of genders, and ages, by using Chi-square-test to evaluate a potential difference. Statistics data between January 1st to November the 4th 2015, was extracted. Number of patients in this group is 11087; among these, 65.4% (7251) females, 34.6% (3836) males; – 97.2% diagnosed with AMD; and 37193 anti-VEGF injections were performed during the time period. Age was divided and distributed into four groups; 104 (<50); 473 (50-64); 5236 (65-80); 5274 (>80); and numbers were after extraction adapted to correspond an equal percentage of patients with AMD in the register. An endophthalmitis rate of 0.00127% was presented in the register, representing 16 cases in Sweden during the past eleven months.

2.4 Statistical analysis of cases and controls

Statistical analysis was performed using SPSS® Statistics software, version 23.0. Medians, mean values, ranges and standard deviations were calculated in applicable variables with the program. The common baseline variables in both groups included total number of injections, age, gender, lens status, eye affected and previous eye surgery. Previous eye surgery was defined as surgery in the eye excluding cataract surgery. Lens status includes phakia or pseudophakia, where pseudophakia equals previously underwent cataract surgery. Non-parametric tests were chosen due to skewed data distribution, ineligible for parametrical tests. Chi-square-test was used to calculate presence of differences in distribution of sex, eye effected, lens status, and previous eye surgery, between the case and control group. Mann-Whitney U test was used to analyse the following: Number of injections until endophthalmitis compared to the total number of injections in each subject in the non-endophthalmitis group; comparison of age at endophthalmitis in the control group at the day of the last injection. Difference in age-distribution between age groups of 65-80 and >80 was calculated with Chi-square-test. Age groups were stratified similarly to the groups of ages in the Swedish Macula Registry. A p-value less than 0.05 was considered statistically significant.
3. Results

3.1 Endophthalmitis group

Thirteen cases of postinjectional endophthalmitis were identified over five years, between January 2011 and August 2015 (Tables 1-3). Among these, 92.3% (12) were female and 7.7% (1) were male. The median age at presentation was 84 years (mean 82.5±8.8, range 69-93). The total incidence and individual incidence for each department of ophthalmology is presented in fig. 1. Year 2011 had a total incidence of 2 per year; Year 2012-2014 – 1 per year; and 8 per year 2015. The increase 2015 includes five cases from Dept. C, two cases from Dept. D, and one case from Dept. E. The increase for Dept. C from 2014 to 2015 is 400%.

Endophthalmitis cases were right-sided in 61.5% (8) and in left-sided 38.5% (5). Previously undergone surgery was in 7.7% (1) of the patients, cataract surgery excluded. Phakic eyes constituted 53.8% (7) and 46.2% (6) were pseudophakic. In control status post-endophthalmitis after various time periods one case went from phakic to aphakic and another one from phakic to pseudophakic, and the rest of the lens statuses remained as before endophthalmitis episode. The total number of injections-median was 8 (mean 13±11.9, range 2-43). Data of total number of injections was missing in 15.4% (2) cases. Average number of days between last injection and presentation of symptoms was 3.3±2.5, ranging from 0-8 days. The average number of days between last injection and diagnosis was 5.2±2.8, ranging from 1-9 days. The last anti-VEGF-agent used before endophthalmitis episode was ranibizumab in 69.2% (9), aflibercept in 23.1% (3), and bevacizumab in 7.7% (1). The overall culture sampling-yielding rate in the cases was 100%. Bacteria isolated was in 61.5% (8) *Staphylococcus aureus*; 30.8% (4) *Staphylococcus epidermidis*; and 7.7% (1) *Streptococcus pneumoniae*. Complete antibiotic susceptibility was seen in 69.2% of the cultures (Table 2). The remaining 30.8% were either resistant or had an intermediate resistance pattern towards one or two specific antibiotics (Table 3).
3.2 Control group
The control group included 56 eyes in 51 patients. The median age of the patients was 80 years (mean 78.9±9.5, range 41-96). The median of total number of injections was 7 and 8 (mean 8.5±6.2, range 1-28). Five patients received same-session bilateral therapy, e.g. ten eyes, and were excluded from the correlation analysis involving calculations of eye affected. Female subjects constituted 64.7% (33) of the control group, and 35.3% (18) were male. Right-sided injections had been performed in 41.1% (23) eyes, and left-sided in 58.9% (33). Previous eye surgery, excluding cataract surgery, had been performed in 10.7% (6); including two patients with previous macular haemorrhage surgery; one corneal transplantation; two patients with previous macula pucker surgery; and one vitrectomy due to vitreous traction.

3.3 Statistical analysis and correlations

3.3.1 Baseline characteristics
No statistically significant differences were seen in the total number of injections ($p=0.418$); age ($p=0.179$); eye affected ($p=0.181$); lens status ($p=0.829$); or previous eye surgery ($p=0.745$). Difference in gender ($p=0.052$) was approximately significant. Baseline characteristics are presented in Table 2. No statistical significance was seen when comparing age groups within the intervals 65-80 years and >80 years ($p=0.217$) (fig. 2).

3.3.2 Secondary control group
No statistical differences were seen between the control group and the secondary control group, between genders ($p=0.917$), nor age distribution ($p=0.145$). Year 2015, eight cases of endophthalmitis are presented in our study, which represents 50% of all registered postinjection endophthalmitis cases in the Swedish Macula Registry (total of 16 cases) January to November 2015.
### 3.4 Tables and figures

#### 3.4.1 Tables 1-3

**Table 1. Differences/comparison between endophthalmitis case group and non-endophthalmitis control group.**

<table>
<thead>
<tr>
<th></th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median</td>
<td>84.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>82.5±8.8</td>
<td>0.179</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>69-93</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of injections</strong></td>
<td>Median</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>13.0±11.9*</td>
<td>0.418</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2-43*</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>92.3% (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>7.7% (1)</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Eye affected</strong></td>
<td>Right</td>
<td>61.5% (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>38.5% (5)</td>
<td>0.181</td>
</tr>
<tr>
<td><strong>Lens status</strong></td>
<td>Phakia</td>
<td>53.8% (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudophakia</td>
<td>46.2% (6)</td>
<td>0.829</td>
</tr>
<tr>
<td><strong>Previous eye surgery†</strong></td>
<td>Yes</td>
<td>7.7% (1)</td>
<td>0.745</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92.3% (12)</td>
<td></td>
</tr>
</tbody>
</table>

* Missing data of two cases.
† 56 eyes; 51 patients.
‡ Cataract surgery excluded

**Table 2. Endophthalmitis group (n=13), additional variables**

<table>
<thead>
<tr>
<th>Postoperative lens status</th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aphakia</td>
<td>7.7% (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phakia</td>
<td>38.5% (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudophakia</td>
<td>53.8% (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-VEGF agent last injected</th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>69.2% (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afiblercept</td>
<td>23.1% (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>7.7% (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days between last injection and symptom presentation</th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.3±2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-8</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Days between last injection and endophthalmitis diagnosis including intervention</th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.2±2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Culture yielding rate**

<table>
<thead>
<tr>
<th></th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>100.0%</td>
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<td></td>
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</tbody>
</table>

**Causative infectious microbe**

<table>
<thead>
<tr>
<th></th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>61.5% (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>30.8% (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>7.7% (1)</td>
<td></td>
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</tbody>
</table>

**Bacterial resistance**

<table>
<thead>
<tr>
<th></th>
<th>Endophthalmitis (n=13)</th>
<th>Controls (n=56†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>30.8% (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69.2% (9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Endophthalmitis group data: Overview of bacteria culture, susceptibility pattern, time from injection to presentation and diagnosis, and clinical outcomes

<table>
<thead>
<tr>
<th>Culture</th>
<th>Susceptibility pattern</th>
<th>Time from injection to presentation (days)</th>
<th>Time from injection to diagnosis (days)</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td></td>
<td>5</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>S. aureus</td>
<td></td>
<td>4</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>S. aureus</td>
<td>R: Ceftazidime</td>
<td>1</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>S. aerueus</td>
<td></td>
<td>1</td>
<td>3</td>
<td>Pseudophakia (surgical complication)</td>
</tr>
<tr>
<td>S. aerueus</td>
<td>I: Vancomycin</td>
<td>8</td>
<td>9</td>
<td>Retinal detachment.</td>
</tr>
<tr>
<td>S. aerueus</td>
<td>I: Vancomycin I: Moxifloxacin</td>
<td>5</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>S. aerueus</td>
<td>I: Vancomycin I: Moxifloxacin</td>
<td>5</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td></td>
<td>1</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td></td>
<td>2</td>
<td>3</td>
<td>Serous retinal detachment. Rubeosis Iridis. Aphakia.</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>R: Fusidic acid</td>
<td>6</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td></td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
Fig. 1 – Number of referred or registered endophthalmitis cases each year within the endophthalmitis uptake area of the Department of Ophthalmology at Örebro University Hospital, including cases per year for each ophthalmological department (de-identified as A-E).

Fig. 2. Distribution of ages between January 2011-august 2015, in the endophthalmitis and non-endophthalmitis (control) group.
4. Discussion and conclusion

4.1 Discussion

According to this report, the number of endophthalmitis cases in our region has risen from around one-two cases per year, to eight cases 2015.

The total number of injections did not seem to affect risk of developing endophthalmitis in our study, hence, there does not seem to be a cumulative increase of risk. No previous studies were found studying the role of total numbers of injections specifically. However, a study by Englander et al. concluded an equally independent risk in every single injection with endophthalmitis after an average of seven injections, although only three patients with endophthalmitis were analysed in the report [15]. In comparison, our study presents a median of eight injections (range 2-43) at the time of endophthalmitis, evaluated from thirteen patients.

No other variables analysed were connected to a risk of developing endophthalmitis except for a non-statistically significant tendency ($p=$0.052) towards difference in distribution of sexes among the groups. Frequencies of females appeared higher in both groups, and females were overrepresented in the endophthalmitis group. Comparisons between the control group and the secondary control group, indicated no existing major differences regarding age and gender. Cao et al. reported male gender as a risk factor for developing endophthalmitis in a large meta-analysis analysing endophthalmitis following cataract surgery [24], which in contrast could not be observed in the present study. In addition, AMD is an eye disease mainly affecting the elderly population and the mean age receiving this type of therapy is relatively high (78.6 years in the control group of this study). Age >85 years has been shown to be a risk factor for developing endophthalmitis after cataract surgery [24], and 38.5% of the endophthalmitis cases in this study were >85 years old, all women. The overrepresentation of females could be explained by the tendency of women becoming older than men in general, which perhaps could explain why more women have acquired the complication. A random coincidence due to the small number of cases could also be a possibility. Nonetheless, it was noted that the percentage of women was higher in the secondary control group regardless of age. Possible factors to this gender difference among AMD patients is mentioned in some previous studies reviewed by J.R. Evans [29], suggesting that female gender is a smaller risk...
factor for developing AMD among older age groups. Hormonal factors as well as the association to age are discussed although still remaining unclear [29].

The anti-VEGF agent bevacizumab is previously reported as one of many possible risk factors in developing bacterial or sterile endophthalmitis. In our study there was only one patient out of thirteen who had bevacizumab injected before developing the complication. Afibercept has become the most commonly injected agent in our region, which means all patients in the primary control group received this agent.

No cases of endophthalmitis after intravitreal injections due to neovascular AMD were excluded during the time period. All endophthalmitis patients within the region get referred to the same clinic, which increases probability that numbers are accurate, leaving only a small risk of unreported cases.

A culture-yielding rate with isolation of bacteria was 100% in the endophthalmitis group, signifying that likely no cases were of non-infectious nature. As a contrast, culture-positive rate among the endophthalmitis patients are reported to be around 52.0% and 59.6% in studies by McCannel [16] and Lyall et al. [2], respectively, where more numbers of cases were reported. There is a slight possibility that patients with non-diagnosed non-infectious endophthalmitis with milder symptoms could have been discarded from our clinic and resolved on its own.

Days between injection and symptom presentation in our study was comparable to previous studies. No associations could be observed between bacterial species, susceptibility pattern, days between injection and symptom presentation and diagnosis, and available data of clinical outcome (table 3). Scarce information of clinical outcomes due to limited access to medical records from other hospitals limits making certain conclusions regarding the final outcome. Access to data of visual outcomes following a period of time after treatment would be useful when viewing at these associations to be able to better evaluate the extents of the complication.
Staphylococcus aureus was in this report isolated in eight cases (61.5%); CNS in four cases (30.8%); and streptococci in one case (7.7%). Compared to other studies the ratio is relatively different with S. aureus as the dominating pathogen in our study compared to larger previous studies where CNS are reported as the most common species, varying between 42.4-65.4%, and S. aureus reported in 0.0-17.9% of cultures [2,16,28]. Causes of this difference could coincide with the relatively small number of the group. Other possibilities involves alterations in conjunctival flora due to repeated use of topical antibiotics which increases resistance [30]; or any type of contamination during the procedure such as inadequate hygiene routines, absence of surgical mask of the treater or talking during procedure [16]. Also, failure to apply antibiotics correctly may influence the risk [2]. Some studies suggest using topical antibiotics before or after procedure may even increase endophthalmitis risk and that povidone-iodine can be used alone because of its antiseptic properties [31,32].

Limiting factors of this study are the retrospective design and the small group of cases. Also, in previous studies few certain patient-related risk factors are known in patients receiving intravitreal factors due to rarity of the complication, which limits statistical power. Larger populations are difficult to obtain in these patient groups unless data derives from multiple centres.

4.2 Conclusion

This study has confirmed that the number of cases of endophthalmitis among patients treated with intravitreal injections due to neovascular AMD are increasing in our region as previously perceived. A tendency towards higher risk among females was seen ($p=0.052$). The total number of injections did not seem to affect the risk of developing endophthalmitis in this study indicating remained safety of continued intravitreal anti-VEGF therapy. There was a 100% culture-positive rate in our study among the infected patients. Staphylococcus aureus was the dominating pathogen compared to previous reports showing a dominance of coagulase-negative staphylococci. Further investigation is warranted to identify sources of increase of endophthalmitis, and future studies should consider possibility for other potential risk factors for the complication.
Acknowledgement

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5. References


Ethical considerations

Due to the retrospective design of this study, there is no possibility to retrieve consent from the subjects for use of already existing data. All of the patients are included in the Swedish Macula Registry and consent was previously retrieved for this specific purpose. This study is a clinical follow-up and a student project, which implies no requirement of requesting ethical permission as long as the data is not published publicly, according to an agreement within Örebro University Hospital and is allowed for use within the department. All of the cases and controls, as well as ophthalmological departments were de-identified during the process of data extraction from medical records. Each patient and each eye were coded and received a separate number. Each department was given a non-related letter as name in this report. As endophthalmitis is a rare complication, the numbers of cases retrieved are generally few; therefore de-identification is essential to ensure anonymity and confidentiality. There is a risk of identifying specific patients and connecting personal data, although none of the presented data is considered personal or sensitive. Collected data is later archived according to existing precepts of Örebro University and handled as confidential data. There are no conflicts of interest, and no funding was obtained for the study. The benefits from the observations and conclusions of this study could potentially be summarised from the suggestions as being useful for future guidance and perhaps change in routines, leading to a lowered incidence and prevention of the very serious complication endophthalmitis.
Letter of intent

Dear editor,

We would like to submit our manuscript entitled *Characteristics in patients with neovascular age-related macular degeneration developing postinjection endophthalmitis* for consideration for publication. This is a retrospective case-control study of patients developing postinjection endophthalmitis following anti-VEGF treatment due to neovascular AMD. A perceived increase of endophthalmitis has been noted within this specific patient group within our region during recent years, which is why this study was performed. The aim was to see if the total number of injections could affect risk of endophthalmitis and also identify other patient-related risk factors. An increasing rate of endophthalmitis was confirmed in our study. None of the investigated characteristics was shown to increase the risk of the complication in our study, except for a tendency towards higher risk among females. We also conclude that further investigation of other potential risk factors is needed due to our findings.

This manuscript describes original work and has not been published elsewhere and is not under consideration by any other journal. The authors have approved the manuscript and its submission to the journal and declare no conflicts of interest.

We look forward to your response.

Kind regards,

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Pressmeddelande

Ökning av endoftalmitfall

Endoftalmit är en mycket sällsynt allvarlig infektion som drabbar ögats inre delar. Bland annat kan patienter som får injektioner i ögat med kärlhämmande medel på grund av en våt variant av åldersrelaterade förändringar i gula fläcken i näthinnan ådra sig denna komplikation. Senaste åren har en ökning av endoftalmeter upplevts inom denna patientgrupp på ögonkliniken vid Universitetssjukhuset Örebro vilket också påvisats i en ny studie som gjorts på ögonkliniken. I samma studie undersöktes olika patientrelaterade faktorer som bland annat inte kunde påvisa att antalet injektioner per öga ökade risken att få endoftalmit. Detta skulle kunna antyda att fortsatt behandling med injektioner skulle vara ett säkert alternativ oavsett antalet behandlingar av ögat sedan tidigare. Hos kvinnor däremot kunde en tendens till ökad risk för infektionen ses vilket däremot ej kan bekräftas med säkerhet på grund av behov av ett bredare vetenskapligt underlag.

Vidare bör anledningen till fallökningen undersökas djupare för att finna en förklaring samt utesluta andra möjliga orsaker som skulle kunna innebära att till exempel lokala rutiner för behandling med injektioner i ögat behöver ses över.

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