ORIGINAL ARTICLE

The Incidence of Endophthalmitis after the Application of Intravitreal Injections in FNKV with Regard to Various Prophylactic Antibiotic Regimens

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SUMMARY

Aim: Comparing the incidence of endophtalmitis at the Ophthalmologic clinic of FNKV after the application of intravitreal injections with regard to various prophylactic antibiotic regimens.
Methodics: Comparing the number of endophtalmitis cases during the period of 2005–2011, when the intravitreal applications were secured by full antibiotic prophylaxis (Floxal)/Oftaquix gtt. 5xd 3 days before the application and 3 days after the application with the years of 2012–2013, when Vigamox gtt. was used during the preparation of the eye before surgery to prevent inflammatory changes.
Results: In the years of 2005–2013, 5005 injections were applied. In total we recorded three cases of endophthalmitis. In all cases, a pars plana vitrectomy with sample collection for culture and microbiological analysis was performed. During the years of 2005–2011, 2 651 injections were applied with two cases of endophtalmitis (0,075%, 1:1 325, both cases culture-negative). During the years of 2012–2013, 2 355 injections were applied with one case of endophtalmitis (0,042 %, 1:2 355, culture-positive).
Conclusion: According to our experience, limited prophylactic antibiotic regimen does not increase the incidence of endophtalmitis in comparison with full prophylactic antibiotic regimen.

Key words: intravitreal injections, antibiotic, endophtalmitis, prophylactic

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INTRODUCTION

In the last few years there has been a marked increase in intravitreal applications, primarily in connection with the use of anti-VEGF (vascular endothelial growth factor) preparations. The main indication for their use is wet form age-related macular degeneration (ARMD), and more recently macular edema complicating retinal vein occlusion and diabetic macular edema. A smaller group is represented by other diagnoses, such as neovascular glaucomas, macular edemas of other etiology, neovascular choroidal membrane of origin other than ARMD etc. Other substances applied to the vitreous cavity in the Czech Republic also include corticosteroids (in the form of triamcinolone acetonide (TMC) solution and in depot form – dexamethasone (Ozurdex)), in particular for the treatment of macular edemas.
Because the number of these procedures is constantly increasing, it is necessary to reckon with certain relatively rare, but nevertheless very serious complications for the prognosis of the eye. One of the most serious and most feared complications is indisputably endophthalmitis (29). A logical measure to reduce the incidence of endotphalmitis was the use of topical antibiotic (ATB) prophylaxis before and after the application of the intravitreal preparation. The original standard schema was the use of ATB drops five times per day, three days before and three days after the application. Despite the fact that this prophylaxis reduces bacterial growth (25), to date no unequivocal data has been published in support of the use of this preventive treatment with regard to reducing the incidence of endophthalmitis (3, 5, 32, 35). In what is probably the largest published study to date, the authors Storey et al. (33) analysed a total of 117 171 applications with a total number of 44 suspected cases of endophthalmitis (0.038%), 1 case per 2663 injections), of which 17 were culture-positive (0.0170, 1 per 5 765 injections). Upon the use of ATB (57 654 applications), there was an incidence of 28 cases of suspected endophthalmitis (0.049%, 1 per 2 059 applications). Without the use of ATB (34 900 applications) there was an incidence of 11 cases (0.032%, 1 per 3 173 applications).
Our study analyses the effect of full and partial ATB prophylaxis following the application of an intravitreal preparation at the Ophthalmology Clinic at the Královské Vinohrady University Hospital (FNKV).

METHOD

This represents a retrospective evaluation of serious inflammatory complications following intravitreal applications at the Ophthalmology Clinic of FNKV. The analysed study sample included all patients who had undergone an application of intravitreal preparations 30Ga by injection – Lucentis, Avastin, TriamHEXAL, Macugen – in the period 2005-2013.
The incidence of endophthalmitis was compared in two groups of patients. In

the first group of patients, the topical ATB Ofloxacin (Floxal) or Levoflaxin (Oftaquix) was used in a standard regimen according to the Summary of Product Characteristics (SPC) for Lucentis five times per day 3 days before and 3 days after the application. In the second evaluated group, Moxifloxacin (Vigamox) was applied three times during the preoperative preparation – first 30 minutes before the application, second 20 minutes before the application and finally immediately before the application. Moxifloxacin was chosen for its good penetration into the chamber fluid and exceptionally high concentration in the chamber fluid 20 minutes after the first dosage – the concentration is higher than the minimum inhibition concentration of the most common pathogens causing endophthalmitis (21, 16, 13, 18). Another reason for the use of moxifloxacin is the potential effect together with povidone iodine and the low resistance of microbial flora (34).

APPLICATION TECHNIQUE

Within the years 2005-2012, all the applications were performed in an operating theatre, since 2013 the procedures have been performed primarily in the application ward at the outpatient section of the clinic. In the first observed period, a total of ten doctors applied the injections, in the second period this was performed by a total of five doctors. Before the procedure each patient was examined and then sent to the nurse for preoperative preparation. Topical anaesthesia was induced using Benoxi drops. After laying on the operating bed, the eye and its surrounding area was thoroughly disinfected with 5 % povidone iodine (Betadine 5%), which was left to act for at least 90 seconds. A sterile facecloth and mouth gag were used individually according to the customs of the attending doctor, all attending doctors used sterile gloves, a mouthpiece and cap. In a limited prophylactic regimen, the last drop of povidone iodine was applied to this area before the actual application by the nurse. After indication of the place of injection at a distance of 3.5 mm or 4.0 mm from the limbus in the lower temporal quadrant, the doctor applied the pharmaceutical by the standard method using a 30Ga needle (fig. 1). All applications were performed without the use of a surgical microscope. After the application, perfusion of the optic nerve was checked microscopically.

We considered endophthalmitis to cover all conditions with a severe intraocular inflammation process which required a surgical solution (i.e. performance of pars plana vitrectomy or application of ATB preparations into the vitreous cavity). The diagnosis was always determined by an experienced vitreoretinal doctor. We classify above all deterioration of visual acuity, pain and vitritis within the image of endophthalmitis following the application of an intravitreal preparation. Also specific for endophthalmitis is the high speed of these changes. Inflammatory manifestations in the anterior chamber are usually present later, and hypopyon need not be present, such as in certain cases of endophthalmitis, for example following cataract surgery.

A condition for the inclusion of a patient into the study sample was intravitreal application within a short time period before the manifestation of the pathology. These patients underwent pars plana vitrectomy as a therapeutic procedure, with the taking of a sample of the vitreous body for microbiological and histological analysis, and ATBs were subsequently applied to the vitreous cavity.

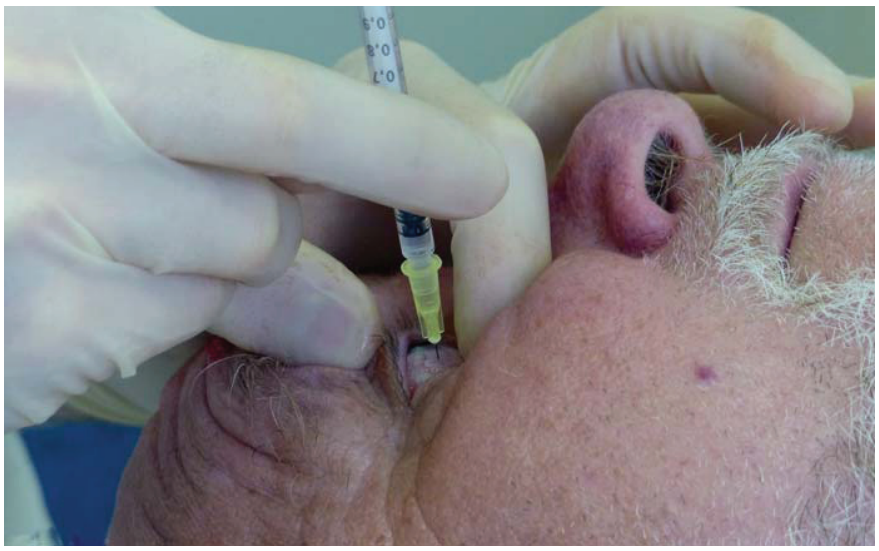


Fig. 1 Technique of intravitreal application

RESULTS

In the first period (2005-2011) – in ATB prophylaxis according to SPC we applied a total of 2651 injuections (1087 x Macugen, 1092 x Lucentis, 101 x TMC, 371 x Avastin (table 1). Within this period, two cases of endophthalmitis were recorded (both following application of the Lucentis preparation). In both cases, the doctor applied the preparation in the operating theatre, in both cases pars plana vitrectomy was performed with a culture-negative microbiological result. The incidence of endophthalmitis with full prophylactic regimen was 2:2 615 in our clinic, i.e. 0.075%.

In the second observed period (2012-2013), in conditions of reduced ATB prophylaxis, we applied a total of 2 355 injections (155 x Macugen, 1650 x Lucentis, 134 x TMC, 415 x Avastin, 1x Eylea), (table 1, graph 1). In 2012 the applications took place in the operating theatre (1 053 injections), in 2013 the intravitreal injections were administered in the application ward at the outpatient section of the clinic (1 302 injections). During this period one case of endophthalmitis was recorded (following injection with the Macugen preparation). The application was performed in the operating theatre. In this case also, pars plana vitrectomy was performed, this time with a cuture-positive finding (Staphylococcus coagulase-negative). The incidence of endophthalmitis with a limited ATB regimen during this period was 2: 23 55, i.e. 0.042%.

DISCUSSION

Today endophthalmitis is indisputably one of the most feared complications following the application of intravitreal preparations, and its course is of absolutely fundamental significance for the future of the eye.

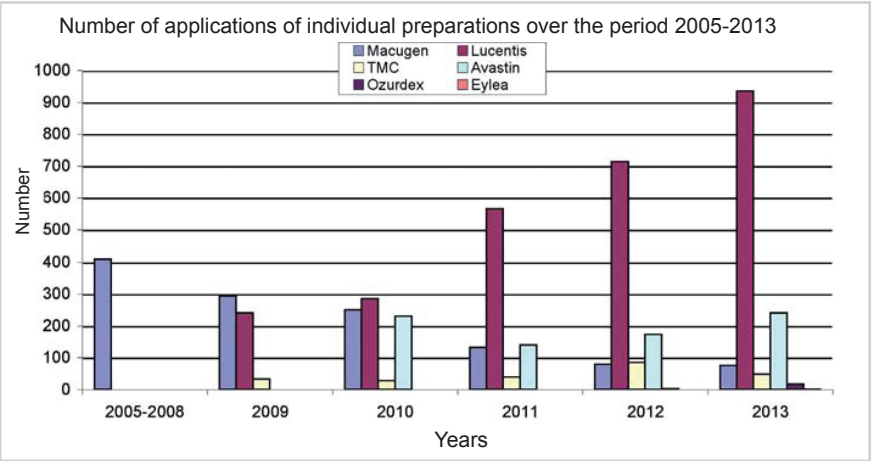
The risk of endophthalmitis following the application of intravitreal preparations differs proportionally in various published studies, from 0.018% to 1.4% (6, 12, 26, 30, 24, 20, 17, 11, 9,

Table 1 number of applications of individual preparations in years 2005-2012

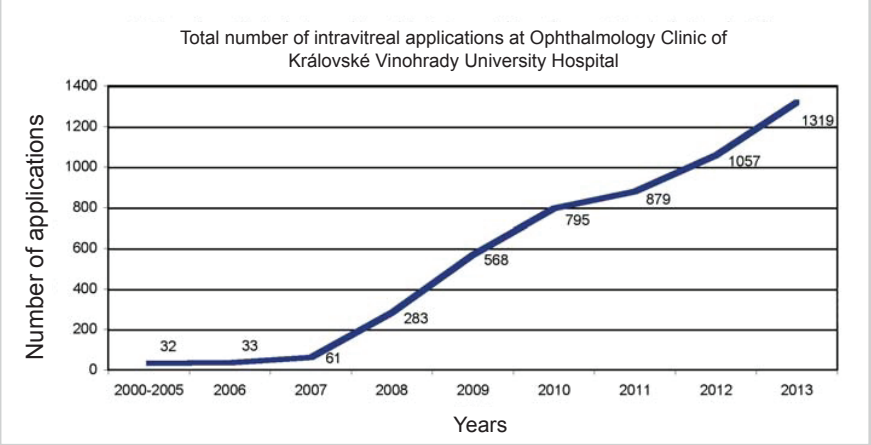
	2005-2008	2009	2010	2011	2012	2013
Macugen	409	294	251	133	79	76
Lucentis	0	241	285	566	714	936
TMC	0	33	28	40	86	48
Avastin	0	0	231	140	174	241
Ozurdex	0	0	0	0	4	17
Eylea	0	0	0	0	0	1
	409	568	795	879	1057	1319

8, 15, 4, 2, 1, 28). For example, in the large prospective studies "The Minimally Classic/Occult Trial of the Anti-VEGF Antibody RAnibizumab in the Treatment of Neovascular AMD (MARINA)" (27) and "Anti-VEGF Antibody for the Treatment of Predominantly Classical Choroidal Neovascularization in AMD (ANCHOR)" (7), the risk of endophthalmitis was 0.05%. The actual definition of endophthalmitis by the individual authors is of great significance for the determination of the frequency of endophthalmitis in the individual studies. In the above-stated studies MARINA and ANCHOR, there were in total a further 24 patients with manifestations of medium-severe intraocular inflammation who were not included in this study sample, but according to the conventions of the workplace the majority of them received ATBs applied into the vitreous cavity upon demonstration of vitritis. If we included these patients into the group of patients with endophthalmitis, the frequency of endophthalmitis in the MARINA study would be 0.22%, and in the ANCHOR study 0.18%, which is an almost four times greater risk than was published.

In recent years, in connection with the wide use of ATBs, there has been frequent talk of an exponential increase in microbiological resistance in all branches of medicine, often with fatal consequences, in particular for otherwise generally weakened patients. The largest share of the blame for creating this situation indisputably lies with the unnecessary overuse of ATBs, and ophthalmology undoubtedly contributes to this situation. In the above-stated two-year studies ANCHOR and MARINA, where the patients applied ATB drops each month before the check-up, there was a high degree of overuse of ATB in our opinion. If we adhered to this schema also in regular practice, especially in the pro re nata (P.R.N.) regimen, each patient would apply ATB drops for at least 36 days per year (3 days x 12 months). This overuse of ATB drops then leads demonstrably to an increase in the resistance of the microbiological flora of the conjunctiva (23), with all the potentially negative consequences.



Graph 1



Graph 2

At a time when the numbers of patients treated for retinal pathologies are constantly increasing (graph 2), with an attendant increase in the numbers of applications of substances to the vitreous body, it is advisable to study the effectiveness of preventive measures against endophthalmitis as the most serious potential complication of this therapy. At various workplaces worldwide today, we encounter diametrically opposite approaches to the application procedure. On the one hand there are workplaces where injections are performed in an operating theatre, the patient is dressed in operating clothing with a cap, the application area is screened off and sterile, a sterile foil is affixed to the eye, the operating surgeon wears a cap, facecloth and uses a sterile empir, sterile gloves are an absolute standard and the application is performed with the use of povidone iodine and several days of prophylactic antibiotic preparation. On the other hand there are workplaces (especially abroad) where the application takes place immediately after indication on an application chair at an outpatient department, frequently without sterile gloves or other special preparation, and the injection may be administered by a nurse (22). Both of these situations have their advantages, either from the perspective of safety in the first case or from the perspective of timeliness of commencement of therapy in the second case; they also have their

disadvantages primarily in the financial, logistical and material securing in the first case, or in the risk of infection complications in the second.

Today several ophthalmologists consider the use of povidone iodine to sterilise the surrounding area of the eye and its surface to be the sole fundamental measure for the prevention of endophthalmitis (31, 26). According to the authors Friedman et al. (10), the time necessary for a significant and sufficient reduction of bacterial flora is 30 seconds. A further observation was that the application of a mouth gag has no influence on the quantity of bacterial flora in the conjunctival sac upon the use of povidone iodine. The study by the authors Chen E LM et al. (14) demonstrated that the majority of microorganisms causing endophthalmitis are commensals of the oral mucous membrane, and as a result both the staff and the patient should avoid speaking or coughing during the application, and that a mouthpiece should be used throughout the entire duration of the application as a prevention against the risk of contamination.

The collective of authors Lam, Waheeb (19) also compared various prophylactic antibiotic regimens. The result was the most favourable in the group of patients who did not use ATBs whatsoever. Upon the use of ATB prophylaxis on the day of application, the incidence of endophthalmitis was the highest – 0.083%, in comparison with 0.061% upon five-day prophylaxis and 0.037% without ATB prophylaxis.

CONCLUSION

If we take into account the fact that there are various studies (3, 5, 32, 35, 19) that refute the significance of ATB prophylaxis before the application of an intravitreal preparation, it is necessary to ask whether or not this prophylaxis is in fact rather harmful to patients.

Although it is stated that it is possible to reach a statistically significant comparison of various regimens upon a comparison of the incidence of endophthalmitis only upon more than 100 000 applications, according to our experiences it is possible to judge that a heightened prophylactic ATB regimen does not reduce the incidence of endophthalmitis following the application of intravitreal preparations, which corresponds with the results of large foreign studies.

With regard to the above-stated studies and our own experiences, all ATB therapy before and after the application of an intravitreal preparation by a 30Ga needle was discontinued at our workplace as of 1 January 2014, and since that time we have continued to ensure only thorough and careful disinfection of the operating field, adherence to regimen measures and handling of the needle.

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