Possibilities of Infection and Increase of Intraocular Pressure After Intravitreal Application of Bevacizumab in Treatment of Exudative Form of AMD

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INTRODUCTION

Tremendous endeavors and investments have been made lately in the research of therapeutic options for treatment of AMD, most of all because this disease is a leading cause of the central blindness in the world in population aged over 65 years. On the other hand, there are no adequate therapeutic modalities, especially not for a treatment of the exudative form of maculopathy, which is the main cause of development of the central blindness. The most modern and most recent AMD treatment modality involves the application of drugs directly injected in the vitreous area of the eye. (1, 2). The following are used:

- Avastin (Bevacizumab) 1.25 mg (0.05 ml) in three doses every two months.
- Lucentis (Ranibizumab) 0.5 mg 1x a month for three months.
- Macugen (Pegaptanib sodium) 0.3 mg in three doses every six weeks. The following complications may occur in a small percentage: suffusions in the bulbar conjunctiva (3, 4), bleeding (hae-
mophthalmus) (5, 6), increased intraocular pressure (7, 8), peeling of the internal membrane of the eye (9, 10), inflammation (endophthalmitis) (11, 12, 13) and rupture of the retina and hori-oidea (14).

2. RESEARCH OBJECTIVE
The goal is to establish the frequency of increase of intraocular pressure and endophthalmitis as well as other complications that may occur after intravitreal application of bevacizumab.

3. SUBJECTS AND RESEARCH METHODS
The research was conducted as a retrospective prospective clinical, manipulative control study. This study included 45 patients, 75 eyes with exudative form of senile degeneration of the macula lutea, who were treated in the General Hospital "Prim. Dr. Abdulah Nakas" during the period from 2007 to 2010.

The criteria for inclusion of patients in the study was that the patients had clinical signs of the senile degeneration of macula lutea with changes in the retina verified by diagnostic methods, and aged between 55 and 75 years. The criteria for exclusion of the patients from the study: the patients who have some other type of eye disease.

3.1. Bevacizumab intravitreally
The intravitreal injection represents direct application of the medicine in the eye in an area where the highest concentration and the strongest effect of the medicine is ensured. (15, 16, 17). The dose of 1.25 mg bevacizumab intravitreally (0.05 ml) is being applied. The procedure is virtually painless, because a very thin and small 27 G needle is used, and the eye is previously anesthetized by anesthetic drops, Tetracaine salt 2x. The procedure is performed in the operating room due to fully sterile conditions. It is measured by caliper, and it is given 3.5 mm from the limbus through the pars plana.

In the first few days after the surgery, the patient may see some floaters floating before the eye. Over the time, usually in 1-3 months, the cure dissolves completely.

3.2. Follow-up examinations
After the application of medicine, the patients use antibiotic drops, Tobrex salt 4x for five days. The patients are being explained that they will see some floaters floating before the eye in the first few days after the surgery. That is the remedy in the vitreous of the eye that will soon settle to the bottom of the eyeball, and it does not cause any further complication.

3.2.1. Intraocular pressure IOP
The intraocular pressure is measured before the application of bevacizumab and after 1st, 2nd and 3rd dose.

3.2.2. Bio-microscopic examination of the anterior eye segment
The bio-microscopic examination is conducted two days after the application of bevacizumab.

4. RESULTS
The above presented table implies that there is no statistically significant difference (Student test, p>0.05) in intraocular pressure for any measuring period.

<table>
<thead>
<tr>
<th>Pressure in mmHg</th>
<th>Start of therapy</th>
<th>1st dose</th>
<th>2nd dose</th>
<th>3rd dose</th>
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Table 1. Intraocular pressure

The bio-microscopic findings indicate changes at certain number of patients. After the first application of medicine, there were 9 suffusions of bulbar conjunctiva in the application area. There were 10 suffusions after the second application. And after the third dose of bevacizumab, there were 5 suffusions and 3 cases of inflammations of the anterior eye segment, anterior uveitis.

5. DISCUSSION
Bevacizumab is a drug that falls within the group of synthetic antibodies against the vascular factor. In case of exudative form of senile macular degeneration, the vascularization, that is newly formed blood vessels, press the center of the clearest vision or the yellow spot, thus causing bleeding of the yellow spot. The application of this drug neutralizes the vascular factor (VEGF) thus preventing formation of new harmful blood vessels.

This research included 45 patients who were treated at the Ophthalmology Department of the General Hospital "Prim. Dr. Abdulah Nakas". Bevacizumab was used to treat 45 patients, 75 eyes. Among them, 36 patients received treatment on their right eye, and 39 patients had their left eye treated. In 30 patients both eyes were treated by bevacizumab, in 6 just the right eye, and in 9 just the left eye.

The bio-microscopic findings indicate changes at certain number of patients. Out of 225 intravitreal injections of bevacizumab, there were 24 suffusions (10.66%) and three inflammations of the anterior eye segment, anterior uveitis (1.33%).

Costa and associates, the most frequent side effects are hyperemia of conjunctiva and suffusion in the area of injection. (18). Ladas and associates, the most frequent side effect after 2.000 intravitreal injections is suffusion of conjunctiva. Out of 2.000 injections, 200 patients had suffusion of conjunctiva (10%). The patients who used to take Aspirin are more inclined to subconjunctival suffusions. In only one patient who received bevacizumab, ablation of retina occurred (0.05%). Eye inflammation (uveitis) was registered in 1.9% patients (4). Artunay and associates, the study included 3022 intravitreal injections of 1.25 mg bevacizumab, and three patients had endophthalmitis. Acute endophthalmitis is still potential complication after intravitreal injection of bevacizumab (approximately 0.066%) (19). Masnom and associates, during 23 month long research, incidence post-injection en-
dophthalmitis rate is 0.019%. Out of 5,233 intravitreal injections of bevacizumab, only one case of endophthalmitis was registered (20). Johnson and associates, total 693 intravitreal injections of bevacizumab have been applied. In 9 patients, intraocular inflammation occurred and the incidence is 1.30% (21). Sato and associates, five (14.3%) of 35 cases had severe intraocular inflammations, and the inflammation had characteristics of the toxic anterior segment syndrome (TASS) (11). Fintak and associates examine the endophthalmitis incidence rate after intravitreal injections. The endophthalmitis rate is low, about 1 in 4 500 injections, which is 0.02% (22).

As for the intraocular pressure, there is no statistically significant difference (p>0.05) for any measuring period. When analyzing the trend line, we can conclude that the trend line is linear. Krebs and associates, the intraocular pressure did not increase after intravitreal injections of bevacizumab. The analysis included 44 patients, of which 21 patients with early lesions and 23 with progressive lesions observed for 6 months (24). Frenkel and associates, increased ocular pressure after intravitreal injection is common, but in most cases, it is temporary. 71 patient received bevacizumab intravitreally; IOP was measured before the injection, within 1 minute after the injection and every 10 minutes until the pressure was normalized (7).

6. CONCLUSION

The bio-microscopic findings in bevacizumab treated group indicate changes at certain number of patients. Out of 225 injections, there were 24 suffusions of the bulbar area of conjunctiva in the area of drug application (10.66%) and three inflammations of the anterior eye segment, anterior uveitis (1.33%). As for the intraocular pressure, there is no statistically significant difference (p>0.05) for any measuring period. When analyzing the trend line, we can conclude that it is linear.

Based on the results achieved in the intravitreal application of bevacizumab in senile degeneration of macula lutea, we can make the following conclusions: Possibility of infection after the intravitreal application of bevacizumab does exist, but it is minimal when working in a sterile environment. Increased intraocular pressure is possible, but not necessarily to happen after the intravitreal application of the medicine.

REFERENCES