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INTRAVITREALNA INJEKCIJA BEVACIZUMABA PRE TRABEKULEKTOMIJE ZA LEČENJE NEOVASKULARNOG GLAUKOMA KOD PACIJENATA SA DIJABETESOM


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INTRAVITREALNA INJEKCIJA BEVACIZUMABA PRE TRABEKULEKTOMIJE ZA LEČENJE NEOVASKULARNOG GLAUKOMA KOD PACIJENATA SA DIJABETESOM


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Abstract

Background/Aim. To evaluate the efficacy and safety of intravitreal injections of Bevacizumab before trabeculectomy with mitomycin C (MMC) for treatment of neovascular glaucoma (NVG). Methods. A prospective and open-label study, from May 2013 to December 2014, was conducted on consecutive NVG patients who underwent intravitreal injections of Bevacizumab and a primary trabeculectomy with MMC. All patients were followed-up at least for 12 months. Success was defined as an intraocular pressure (IOP) of ≤21 mm Hg with or without topical ocular hypotensive medication.

Results. Fourteen eyes of 12 diabetic patients fulfilled the respective demands of the inclusion and exclusion criteria. The mean (standard deviation) follow-up period was 15.0 (2.0) months (range, 12 to 19 months). After one year of follow-up, 11 (78.6%) eyes had an IOP ≤ 21 mmHg. The mean IOP was significantly reduced from 42.4 (9.7) mmHg preoperatively to 18.4 (2.9) postoperatively, p<0.0001. Regarding surgical complications, hyphaema was observed in 3 (21.4%) eyes, macular edema in one eye (7.1%) after 6 months of trabeculectomy, and recurrence of neovascularization requiring intravitreal Bevacizumab injection in 2 eyes (14.2%) after 6 months. Conclusion. Preoperative intravitreal bevacizumab may be effective as adjunctive treatment for trabeculectomy with mitomycin-C for neovascular glaucoma patients.

Key words: bevacizumab; diabetes. mitomycin -c. neovascular glaucoma. trabeculectomy.
new vessels across the scleral spur and subsequent obstruction of the trabecular meshwork. The new blood vessels are usually accompanied by a fibrous membrane, and contraction of this membrane results in formation of peripheral anterior synechiae and progressive angle closure. Neovascularization is caused by proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), and ocular ischemic syndrome (OIS) [1]. Surgical procedures such as trabeculectomy with antimetabolite agents, are often used to manage elevated intraocular pressure in NVG patients. Intraoperative mitomycin-C during trabeculectomy (TMC) may be considered as the gold standard for glaucoma surgical treatment [2].

Anti-vascular endothelial growth factor (anti-VEGF) represents an alternative treatment for neovascular glaucoma [3, 4]. Intravitreal bevacizumab (IVB; Avastin, Genentech, Inc.,San Francisco, CA, USA) injection has been shown to reduce ocular neovascularization and vascular permeability in patients with ischemic retinal diseases and age-related macular degeneration, firstly reported in 2006 [5, 6]. Additionally, IVB caused regression in the anterior chamber angle neovascularization, providing better intraocular pressure (IOP) control in NVG patients in open angle stage [7, 8]. The aim of this study was to evaluate the efficacy and safety of intravitreal injections of bevacizumab, administered preoperatively, as adjunctive therapy for trabeculectomy with mitomycin-C in neovascular glaucoma patients.

**Methods**
A prospective and open-label study, from May 2013 to December 2014, was conducted on consecutive patients with NVG who underwent a TMC with preoperative intravitreal application of Bevacizumab. Recruitment was ongoing for a period of 6 months with aim to collect a sufficient number of patients. The off-label use of bevacizumab (Avastin; Roche Pharmaceuticals, Basel, Switzerland) was also approved by the institutional review board (IRB) of the University Eye clinic, ClinicalCentre of Serbia. Written informed consent about the glaucoma treatment was obtained from all patients after thorough discussion of the potential benefits and risks of intraocular bevacizumab injection.

Neovascular glaucoma was defined as the presence of iris and/or anterior chamber angle neovascularization with extensive fibrous synechiae (at least 2/3 of the angle area) in the angle and an IOP equal or higher than 21 mm Hg with antiglaucoma medication, either topical or systemic. Eyes with no light perception were excluded from this study.

**Procedures**
Neovascular glaucoma patients who were included in the study before arriving at our glaucoma department on surgery had several retinal photocoagulation (standard spot size 200µm, 300-400 spots per treatment, average 3 sessions and average 2100 spots) sessions covering average 2/3 of retina, but not complete panretinal photocoagulation before neovascular glaucoma forming.

Intravitreal injection of 50ml (1.25mg; ec. 0.5 mg/0.05 ml) of bevacizumab through 30 G needle inserted through the pars plana, under topical anesthesia with 4% lidocaine (tetracaine). Monitoring of regression of iris neovascularization lasted for two weeks. A fornix-based conjunctival flap technique for trabeculectomy with 0.2 mg/ml mitomycin C was performed within 2 weeks-1 month after IVB.
Trabeculectomy was performed by the same experienced surgeon (IM). The trabeculectomy procedure included creation of a fornix-based conjunctival flap and a 3x4-mm, half-thickness scleral flap. Small pieces of surgical sponge soaked in 0.2 mg/ml mitomycin-C were then inserted under the conjunctival flap for up to 2 minutes. Trabeculectomy was done with a Kelly Descemet’s Membrane Punch (Inami, Tokyo, Japan). After that a peripheral iridectomy. The scleral flaps were closed with 10–0 nylon sutures, and the conjunctival flap was closed with an 8.0 absorbable suture.

The visual acuity, IOP, anti-glaucoma medications, and the appearance of the iris neovascularization (NVI) by ophthalmoscopy were compared at baseline and post-IVB and before (pre-trab) and after (post-trab) trabeculectomy. The intraoperative and postoperative complications were also recorded.

Postoperatively patients were examined at day 1, day 7th, every month till month 3, and every 3 months thereafter.

IOP was measured by Goldmann applanation tonometry. The mean of two IOP measurements immediately before trabeculectomy were adopted as the preoperative IOP. Surgical success was defined as an intraocular pressure (IOP) of ≤21 mm Hg with or without topical ocular hypotensive medication. On the other hand, surgical failure was defined as insufficient IOP reduction (IOP ≥22 mmHg, ≤20% IOP reduction, use of a systemic carbonic anhydrase inhibitor, or further glaucoma surgeries), devastating complications (loss of light perception, phthisis bulbi, and endophthalmitis), or significant hypotony (IOP equal or lower than 5 mmHg continuing six months and until the last follow-up visit or hypotony that required intervention).

Statistical Analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics 20, IBM Corp., New York) and Stata software (version 13.1; StataCorp, TX). Descriptive statistics (mean [standard deviation]) and 95 % Confidence intervals (95% CIs) were used for demographic and clinical characteristics.

Data were tested for normal distribution using the Kolmogorov-Smirnov test. For comparisons between baseline and post-IVB, and for pre-trab and post-trab; mixed-effects models using clustered robust standard errors by Stata software were used to account for the correlation of both eyes in the same patient. For all analyses, a P-value of <0.05 was considered statistically significant.

Results

Fourteen eyes of 12 diabetic patients were included in the study. Their main clinical and demographic characteristics are shown in Table 1.

Two weeks post-injection, all cases showed complete regression of the iris an angle new vessels. Recurrence of iris neovascularization was observed in 2 (14.2%) eyes at month 6 where reinjection was done; a second recurrence of neovascularization was not observed. The mean (standard deviation) (SD) follow-up period was 15.0 (2.0) months (range, 12 to 19 months).

The mean (SD) preoperative IOP was 42.4 (9.7) mmHg. TMC significantly reduced IOP at all time point measurements, p<0.0001, respectively (Figure 1).

After one year of follow-up, 11 (78.6%) eyes had an IOP ≤ 21 mmHg and were considered as success.
The mean (SD) number of antiglaucoma medications at baseline was significantly higher, 3.0 (0.0) than that reported at month 12, 1.1 (1.5), p=0.0003. Visual acuity did not show any significant change between pre-trab measurements [0.35 (0.3)] and after one year of follow-up [0.40 (0.3)], p=0.1500.

As regards complications, hyphaema was seen in 3 (21.43%) eyes at the early postoperative; at month 6, one (7.1%) patient had macular edema and 2 (14.2%) eyes showed recurrence of neovascularization requiring intravitreal Bevacizumab injection.

**Discussion**

The results of our study suggested that intravitreal injections of bevacizumab, administered preoperatively, as adjunctive therapy for trabeculectomy with mitomycin-C in neovascular glaucoma patients is effective not only for reducing IOP but also for preventing bleeding. Additionally, our study also found a complete regression of the iris neovascularization in all the eyes 2 weeks after IVB injection. These results are in agreement with Iliev et al [3] and Marey & Ellakwa [9] who reported complete regression of neovascularization at the end of follow-up period in 100% of cases. Conversely, Oshima et al [7] observed complete regression in 29% only of their cases.

The rate of reinjection is lower than that reported by Oshima et al [7] (29% at month 2) and Marey & Ellakwa [9] (20% at month 4 and 70% at month 8).

The success rate of trabeculectomy with MMC in NVG is quite low [10]. In our study, 11 (78.6%) eyes had an IOP ≤ 21 mmHg after 12 months of follow-up. These results are in line with those reported by Marey & Ellakwa [9] who reported a success rate of the 77.8%. However, it is slightly lower than that observed by Elmekawey & Khafagy [11], who found a success rate (IOP between 10 and 21 mm Hg with or without medication) of the 90%, but using ranibizumab as adjunctive therapy for the TMC.

Regarding visual acuity, our study did not find any significant improvement after treatment, this in contradiction with Marey & Ellakwa [9] who observed a significant improvement of the visual acuity; p=0.0001.

This study has some limitations that should be mentioned; among them is its open-label design. Nevertheless, the fact that the statistical analyses were conducted in a masked fashion may have reduced the potential for bias. Another limitation is that this is a single center study with a limited number of patients.

**Conclusion**

Despite these limitations, this study found that intravitreal bevacizumab, administered preoperatively, as adjunctive therapy for trabeculectomy with mitomycin-C in neovascular glaucoma patients, not only successfully produce regression of iris neovascularization but also increase the success rate of the trabeculectomy with mitomycin-C. Further studies are needed to elucidate the long term effect of trabeculectomy with adjunctive bevacizumab injections in neovascular glaucoma patients.

Acknowledgements: none.
References

### Table 1.
Baseline demographic and clinical characteristics. Fourteen eyes of 12 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD) 57.3 (12.0)</td>
</tr>
<tr>
<td></td>
<td>Range 28 – 69</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 9 (75.0%)</td>
</tr>
<tr>
<td></td>
<td>Female 3 (25.0%)</td>
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<tr>
<td>Pre-trabeculectomy IOP, mm Hg</td>
<td>Mean (SD) 42.4 (9.7)</td>
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<tr>
<td></td>
<td>Range 30 – 69</td>
</tr>
<tr>
<td>Pre- Trabeculectomy VA</td>
<td>Mean (SD) 0.35 (0.30)</td>
</tr>
<tr>
<td></td>
<td>Range 0.01 – 0.5</td>
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<tr>
<td>Antiglaucoma medications, n (%)</td>
<td>Beta-blockers 14 (100%)</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin analogues 14 (100%)</td>
</tr>
<tr>
<td></td>
<td>CAI 14 (100%)</td>
</tr>
<tr>
<td>Systemic medications, n (%)</td>
<td>HBP 12 (100%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes 12 (100%)</td>
</tr>
</tbody>
</table>

SD=Standard deviation; n= Number; IOP= Intraocular pressure; VA= Visual acuity; CAI= Carbonic anhydrase inhibitors; HBP= High blood pressure
Figure 1. Evolution of intraocular pressure (IOP) over the length of follow-up. The mean IOP, at all points measured, was significantly lower than the pre-trabeculectomy IOP, p<0.0001.

Abbreviations:
Pre-trab= Pre-trabeculectomy; D= day; W= Week; M=Month

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