ORIGINAL STUDIES

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PHARMACOLOGICAL INTRAVITREAL TREATMENT FOR MACULAR EDEMA IN BRANCH RETINAL VEIN OCCLUSION – THREE-MONTH RESULTS

FARMAKOLOŠKO INTRAVITREALNO LEČENJE EDEMA MAKULE KOD OKLUZIJE GRANE CENTRALNE VENE RETINE – TROMESEČNI REZULTATI

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Summary

Introduction. Macular edema is the main cause of visual loss in patients with branch retinal vein occlusion. Macular edema is initially reversible, but over time, permanent loss of vision occurs from structural damage to the macula. For this reason, there is a need for more rapid and effective treatments than laser photocoagulation which has been established as a gold standard. There are several pharmacologic agents which have changed the management of macular edema. Material and Methods. Twenty eyes of 20 consecutive patients of the Department of Eye Diseases, Clinical Center of Vojvodina, in Novi Sad, were enrolled in this prospective, randomized and consecutive study conducted from January 2012 to January 2013. The patients were randomly assigned into two treatment groups, and they were given an intravitreal injection of bevacizumab 1.25 mg/0.05 mL (Avastin®), or triamcinolone acetonid injection 4 mg/0.1mL (Kenalog®). Re-injections were performed according to the following retreatment criteria: a loss of visual acuity or increase in central retinal thickness. Results. Both intravitreal bevacizumab and triamcinolone-acetonid were very effective in reducing macular edema and improving visual acuity in the eyes with macular edema secondary to retinal vein occlusion. The effect of the treatment was more pronounced if it started early after the onset of macular edema. The reported temporary effects of intravitreal triamcinolone-acetonide and bevacizumab could be explained by their clearance from the eye. Conclusion. The short-term results of our clinical trial showed that pharmacological intravitreal agents, such as bevacizumab and triamcinolone-acetonid, lead to rapid resolution of macular edema and significant improvement of visual acuity.

Key words: Macular Edema; Intravitreal Injections; Retinal Vein Occlusion; Treatment Outcome

Sažetak


Ključne reči: Makularni edem; Intravitrealne injekcije; Okluzija retinalne vene; Ishod lečenja
Introduction

Branch retinal vein occlusion (BRVO) is a common retinal vascular occlusive disorder with the incidence of 2.14/1000/year in individuals over 40 years of age [1]. It may cause sudden vision loss because of blood nonperfusion and retinal hypoxia. In later stages, it is often complicated with macular edema (ME) which may cause an additional visual reduction that often exceeds the previous ischemic damage, and thus macular edema represents an important treatment target [2].

Macular edema is considered to be the major reason of visual impairment in BRVO [3, 4]. ME is initially reversible, but over time, permanent loss of vision occurs due to structural damage to the macula. Treatment options for the ME have changed through the years. Branch Vein Occlusion Study Group reported in 1984 that grid laser photocoagulation was superior in improving visual acuity compared to the observation. However, most patients had moderate visual acuity improvement after laser treatment [4]. In addition to possible complications associated with laser photocoagulation [5–9], the presence of intraretinal hemorrhages in the macula postpones the beginning of the laser treatment for several months [10], which compromises the functional outcome of this treatment. For this reason, there was a need for more rapid and effective treatments that could provide better functional and anatomic outcome [11].

In recent years, intravitreal pharmacologic agents have been used with increasing frequency in the treatment of retina vein occlusion and have changed the approach in dealing with ME [12]. Their anti-inflammatory and anti-angiogenic effects target vascular permeability, reduce ME and thus improve the vision [13]. Currently, there are several pharmacologic agents used for ME caused by BRVO. Some of them are approved by the United States Food and Drug Administration (USFDA), including intravitreal dexamethasone implant (Ozurdex®, Allergan) and ranibizumab (Lucentis®, Genentech), while intravitreal bevacizumab (Avastin®, Genentech) and triamcinolone acetonid (Kenalog®, Allergan) have been used off label [12].

Several studies have reported the effectiveness of intravitreal injection of triamcinolone acetonide (TA) [14–16] and of anti-vascular endothelial growth factor (VEGF) agents, such as bevacizumab, in dealing with ME caused by BRVO [17, 18]. Considering these promising preliminary results, the aim of our study was to compare the effectiveness and safety of intravitreal bevacizumab (Avastin®) 1.25 mg/0.05 ml and intravitreal triamcinolone acetonide (Kenalog®) 4 mg/0.1ml in the eyes with macular edema due to branch retinal vein occlusion.

Material and Methods

Twenty eyes of 20 consecutive patients of the Department of Eye Diseases, Clinical Center of Vojvodina, in Novi Sad were included in this prospective, randomized and consecutive study between January 2012 and January 2013. The patients were randomly assigned into two treatment groups. In one group, the patients were given an intravitreal injection of bevacizumab 1.25 mg/0.05 mL (Avastin®, while the second group patients were administered a triamcinolone acetonid injection 4 mg/0.1 ml (Kenalog®). We named group one as intravitreal bevacizumab (IVBe) group, and group two as IVTA (intravitreal triamcinolone-acetonid) group.

All patients underwent complete baseline ophthalmological examination including medical history, visual acuity assessment (measured by Snellen chart), applanation tonometry, slit lamp examination, dilated fundus examination with indirect ophthalmoscopy, fluorescein angiography (FA) and biochemical investigations such as complete blood count, prothrombin time, partial thromboplastin time, random blood sugar, renal function tests, liver function tests and erythrocyte sedimentation rate. The diagnosis of ME was confirmed by OCT and FA.

The inclusion criteria were: the patients with ME caused by BRVO, and no disc or retinal neovascularization. The exclusion criteria were: previous laser photocoagulation, intravitreal injections or vitrectomy, significant media opacity, and contraindications for bevacizumab or TA. The patients were initially followed up at the first post-injection day and then at four, six and twelve weeks after injection. Re-injections were performed according to the following retreatment criteria: the loss of visual acuity or increase in central retinal thickness (CRT) on OCT, compared with the best values after the initiation phase. All patients were observed for 12 weeks for further status and additional treatments. Informed consent was obtained from each patient after discussing about the benefits and possible risks of these two drugs. The study was approved by the Ethics Committee of the Clinical Center of Novi Sad. The main outcome measures included changes in the best-corrected visual acuity (BCVA) and the central retinal thickness (CRT) during follow-up examinations, and postoperative complications.

Data were analyzed using SPSS 15.0. Baseline demographic and clinical parameters were compared between the two groups using independent-samples T-test for numerical variables (such as changes in BCVA.

Abbreviations

BRVO – branch retinal vein occlusion
ME – macular edema
TA – triamcinolone acetonide
IVBe – intravitreal bevacizumab group
IVTA – intravitreal triamcinolone-acetonid group.
OCT – optical coherence tomography
FA – fluorescein angiography
CRT – central retinal thickness
BCVA – best-corrected visual acuity
IOP – intraocular pressure
VEGF – vascular endothelial grown factor
RVO – retinal vein occlusion
Table 1. The baseline characteristics of two treatment groups with regard to patients’ sex, age, time until the first injection, pretreatment visual acuity and retinal thickness.

<table>
<thead>
<tr>
<th></th>
<th>IVBe group</th>
<th>IVTA group</th>
<th>p value Vrednost p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients/Broj pacijenata</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)/Pol (M : Z)</td>
<td>8:3</td>
<td>4:5</td>
<td>0.205</td>
</tr>
<tr>
<td>Age (years)/Starost (godine)</td>
<td>61.54±7.679</td>
<td>59.33±7.257</td>
<td>0.541</td>
</tr>
<tr>
<td>Time until the 1st injection (month)/Vreme do 1. injekcije (meseci)</td>
<td>3.45±2.270</td>
<td>4.33±1.4907</td>
<td>0.356</td>
</tr>
<tr>
<td>Pretreatment BCVA/Predretman</td>
<td>0.4±0.112</td>
<td>0.355±0.177</td>
<td>0.527</td>
</tr>
<tr>
<td>Pretreatment/CRT (μm) Predretman</td>
<td>416.54±67.906</td>
<td>442.77±102.201</td>
<td>0.523</td>
</tr>
</tbody>
</table>

| BCVA - okluzija grane centralne vene retine; CRT - centralna debljina retine; IVBe - intravitrealna injekcija bevacizumata; IVTA - intravitrealna injekcija triaminolon-acetonida |

and CRT). A probability value (p) of less than 0.05 was considered to be statistically significant.

Results

The baseline characteristics by groups are matched and presented in Table 1. As shown, there was no statistically significant difference between the groups with regard to the patients’ age, gender, time from vascular attack until first injection, baseline best corrected visual acuity, and baseline central retinal thickness. The study involved a total of 20 patients (12 men and 8 women) who fulfilled the inclusion criteria. There were 11 patients in IVBe group (55%), and 9 patients in IVTA group (45%). The mean age of patients in the IVBe group was 59.33±7.257 years and 61.54±7.697 years in the IVTA group, (p=0.541). The time from the BRVO appearance until the application of the first intravitreal injection was 3.454±2.270 months in the IVBe group, and 4.333±1.4907 in the IVTA group (p=0.356). There were ten patients in IVBe group (90.90%) and nine patients in IVTA group (100%) who had a history of hypertension, and were treated with oral systemic anti-hypertensive drugs. Two patients in IVBe and four patients in IVTA group (63.63% vs. 77.77%) had diabetes mellitus.

In the IVBe group, the best corrected visual acuity improved significantly (p<0.001) from 0.4±0.112 pre-injection to 0.75±0.137, 4 weeks after the first injection. Visual acuity was still improved 0.881±0.140 8 weeks after the treatment, but the mean BCVA decreased slightly to 0.845±0.130 12 weeks after the treatment although it was still significantly better compared with initial BCVA (p<0.001). In the IVTA group, visual acuity measurements also improved significantly (p<0.001) from 0.35±0.177 pre-injection to a final BCVA of 0.68±0.196, 0.8±0.1563 and 0.855±0.157, 4, 8 and 12 weeks after injection, respectively. Changes in the BCVA did not differ statistically significantly between two treatment groups (F = 0.606, p = 0.614) (Graph 1).

In the IVBe group, ME demonstrated by foveal thickness on OCT improved after treatment (p<0.001). The mean foveal thickness was 416.54±67.906 μm before injection, but after injection, the central retinal thickness decreased significantly to 240.36±49.0 μm and 193.00±26.94 μm four and eight weeks after injection, respectively (-176.18 μm and -223.55 μm, respectively; p<0.001 each). The mean CRT was 203.90±44.11 (-212.64 μm, p<0.001) 12 weeks after treatment, which was little higher than the CRT after eight weeks but yet significantly below compared with the initial CRT (p<0.001). In the IVTA group, the changes of the foveal thickness measured between baseline and postoperative data also showed significant resolution (p<0.001). The foveal thickness was 442.77±102.201 μm before injection, while 4, 8 and 12 weeks after injection, the foveal thickness was 267.44±57.12, 232±49.83 and 220±45.22 μm, respectively. Between-group comparisons with respect to changes in the foveal thickness showed no statistically significant differences (F = 0.225, p = 0.879) (Graph 2).

During the follow-ups, some of the patients showed recurrence of intraretinal edema which was, besides the loss of vision, criterion for re-injections. In the IVBe group, ten patients received re-injection of bevacizumab once (90.9%), five patients (45.4%) received re-injections twice, and two patients (18.1%) received re-injection three times within the 12 weeks of the follow-up period. None of the patients in the IVTA group received a re-injection during the 12 week follow-up. In this study, five patients (55.55%) in the IVTA group had transient elevated intraocular pressure (IOP>22 mmHg). All five patients with increased IOP were successfully treated and controlled with topical anti-glaucoma medication by the end of the study.

Discussion

The short-term results of our clinical trial have shown that pharmacological intravitreal agents for macular edema such as bevacizumab and TA lead to rapid resolution of CRT and significant improvement...
of visual acuity. Several treatment modalities for ME have been investigated and compared in the last years, including laser treatment, intravitreal injections of steroids and anti-VEGF drugs and surgery [19].

In BRVO, the aqueous levels of VEGF and interleukin 6 are related with the extent of retinal ischemia and the severity of ME. Thereby, inhibition of VEGF could have its role in dealing with ME [20]. The most frequently used doses of bevacizumab were 1.25 mg and 2.5 mg, although the published papers suggest that there are no significant differences in efficacy between these two doses [21]. Intravitreal TA injection is commonly used in treating ME of different etiologies [22–24] because TA has potent anti-permeable, anti-VEGF and anti-inflammatory role [25–28]. The exact dose of TA is still unclear although it has been reported that doses from 4 mg to 25 mg are effective [20]. Several retrospective [14, 29] and prospective studies [15, 16] have evaluated the therapeutic effect of 4-mg intravitreal TA for the patients with ME secondary to BRVO. These studies have shown a significant anatomical and functional improvement after intravitreal injection of TA, i.e. a reduction in ME and improvement of visual acuity. The findings obtained in this study are in agreement with previously published results. Pai et al. first used intravitreal bevacizumab as a treatment for ME related to BRVO [30]. Thereafter, there have been several retrospective case series and prospective comparative studies [31–33] examining the effects of bevacizumab in the patients with RVO. The available studies showed the results which were similar to our study, i.e. they demonstrated that intravitreal bevacizumab was very effective in reducing ME and improving visual acuity in the eyes with ME secondary to retinal vein occlusion [12].

The time between occlusion and the beginning of the treatment is a critical factor which determines the therapeutic effect of intravitreal medication. The studies which have included and treated patients shortly after the onset of vascular attack might find better response to treatment than trials including old RVO with chronic ME [13]. Kriechbaum et al. found that short duration of disease had a better visual prognosis than longstanding pathology [32]. Immediate treatment is likely to prevent macular tissue damage from chronic edema by more rapid resolution of intraretinal fluid [34]. Hence, it could be concluded that the effect of treatment is better if the treatment starts soon after the onset of ME, before the macular damage occurs.

The reported temporary effects of intravitreal TA and bevacizumab could be explained by their clearance from the eye [11]. Beer et al. showed that the half-life after 4mg of intravitreal injection of TA was 18.6 days in non-vitrectomized eyes [34], while Krohne et al. said that the half-life of 1.5 mg intravitreal injection of bevacizumab was 9.82 days in non-vitrectomized human eyes [35]. In the current study, during the 12 week follow up, approximately 90% of the patients who had received intravitreal bevacizumab needed repeated injection. No additional treatments were required during the initial 12 weeks after the first injection of TA. This difference was probably due to a short follow-up period and different clearance time of these agents from the eye. Longer clearance time of intravitreal TA from the eye seems to reduce the numbers of re-injections compared to intravitreal bevacizumab [11].

The intravitreal injections of bevacizumab or TA are both relatively well tolerated with no frequent severe side effects [37]. In our study, five of nine BRVO patients without preexisting glaucoma developed steroid-induced elevated IOP after intravitreal TA injection and all were successfully controlled with topical anti-glaucomatous eye drops and none of the patients required surgical intervention. In the IVBe group, the IOP was normal after intravitreal injection. Therefore, intravitreal bevacizumab was safer than intravitreal TA in terms of IOP elevation [38].

Today, it is widely accepted that the quality of life and treatment satisfaction are the measures of the
outcome of every medical treatment [39]. For that reason, present and new instruments for the assessment of the vision quality of life and treatment satisfaction should be applied in the future clinical trials in dealing with macular edema caused by BRVO.

Conclusion

For a long time, a laser photoagulation was the gold standard for treating macular edema caused by branch retinal vein occlusion. Recently, the introduction of pharmacological intravitreal agents has changed the approach to macular edema treatment. The necessity for a more rapid treatment and better anatomical and functional success completely replaced long-accepted laser treatment by intravitreal pharmacological agents (corticosteroids and anti-vascular endothelial growth factor agents) as the first line treatment. Our study showed that both intravitreal agents were very effective in treating the patients with macular edema during the period of three months. However, future randomized controlled clinical trials with larger study samples, longer follow-up periods, and standardized protocols with an appropriate control group are required to compare specific intravitreal agents as well as to determine retreatment strategies for branch retinal vein occlusion related macular edema.

Literatura


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