Original Article

The Effect of Intravitreal Bevacizumab on Central Serous Chorioretinopathy

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ABSTRACT

The aim of this study was to investigate the efficacy of Intravitreal Injection of Bevacizumab (IVB) in patients with Central Serous Chorioretinopathy (CSC) compared to the control group, after four months of injection.

In this study, 30 eyes of 30 patients with CSC, who were in the age range of 23 to 50 years old (70% male subject) were included. Eligible patients were randomly allocated to the intervention (n = 15) and control groups (n = 15). Patients in the intervention group received a single dose injection of bevacizumab (1.25 mg in 0.05 mL), while patients in the control group were followed-up during the same time interval, without any medical interventions. Corrected Distance Visual Acuity (CDVA) and Central Macular Thickness (CMT) were evaluated as the primary outcome measures at the four-month follow-up.

There was no statistically significant difference between the intervention and control groups regarding their baseline characteristics. Corrected Distance Visual Acuity was improved significantly in the intervention group (P < 0.001), while this improvement was not observed in the control group. Furthermore, greater improvement of CDVA was detected in the IVB group compared to the patients without injection (P = 0.018). The CMT findings were in line with CDVA changes in both groups, revealing a significant reduction of CMT only in the intervention group (P < 0.001). Also, thinner central retina was found in the intervention group compared to the comparison group, at the four-month follow-up (P < 0.001). Based on the findings, bevacizumab could be effective for improvement of both anatomical and functional outcomes in patients with CSC.

KEY WORDS

Central Serous Chorioretinopathy; Bevacizumab; Corrected Distance Visual Acuity; Central Macular Thickness ©2018, Med Hypothesis Discov Innov Ophthalmol.

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INTRODUCTION

Central Serous Chorioretinopathy (CSC) is an idiopathic ocular disease that results from serous neurosensory retinal detachment at the posterior pole of the retina, due to the abnormal function of the Retinal Pigmented Epithelium (RPE) [1, 2]. Although choriocapillaris involvement is a primary pathologic ocular finding, yet fluid accumulation was shown to increase resulting from other abnormalities occurring in the RPE and choroidal tissue [3]. Although the main etiology of CSC is unknown, the recent literature has also shown increased choroidal thickness in such patients [1, 4].

Based on the literature, greater incidence of CSC has been reported among males in the age range of 25 to 55 years old. Regarding geographical distribution, white people, Hispanics, and Asian individuals show high prevalence of CSC, while African Americans show the least prevalence of CSC. Subjects, who have been under major stressful conditions, or cases with high blood pressure, positive history of corticosteroids usage, and also pregnant females are at a higher risk of CSC [2, 5].

Complaints of sudden vision loss, micropsia, metamorphopsia, and difficulty in colour perception could be considered as common visual symptoms in these patients [2]. Clinical diagnosis could be achieved based on the ophthalmic examination and also retinal imaging, including Fluorescein Angiography (FAG) and Optical Coherence Tomography (OCT) [6, 7].

In this regard, various therapeutic modalities have been proposed by different reports, although some retina specialists believe that CSC could be resolved spontaneously in 80% to 90% of patients, during a period of three to four months, without any medical intervention [8]. However, in routine ophthalmic practice, laser photocoagulation, photodynamic therapy or intravitreal injection of anti-Vascular Endothelial Growth Factors (anti-VEGF), like Bevacizumab (IVB), have been proposed by other ophthalmologists [9, 10].

According to the literature, the level of both cytokinins and VEGFs are increased in patients with CSC [11], therefore, anti-VEGFs, including ranibizumab and bevacizumab, can be investigated in patients with CSC. It is evident that ranibizumab can penetrate in the retina with greater influence due to its smaller molecular size and higher binding affinity for VEGF, however, Kim et al. did not report on such findings [12]. In this regard, the positive effect of bevacizumab has been found in some clinical trials, revealing improvement in both functional and anatomical findings [13-18], however, it was not found to be effective for treatment of CSC in a meta-analysis by Chung et al. [19]. Although Park et al. [20] did not find any difference between cases injected with IVB and those, who were only followed-up without any treatment, they found that it could accelerate the spontaneous absorption of sub-retinal fluid and decrease the probability of degeneration of photoreceptor cells.

In the present pilot Randomized Clinical Trial (RCT), the researchers aimed at investigating the efficacy of IVB injection in patients with CSC, compared to patients in the comparison group, after four months of injection.

MATREIALS AND METHODS

Participants

In this pilot RCT, a total of 30 eyes of 30 patients, with CSC and an age range of 23 to 50 years old, were included. Sampling was performed among patients that had referred to the Alzahra Eye Hospital, Zahedan University of Medical Sciences, between January, 2015 and April, 2017. The study adhered to the Deceleration of Helsinki and was approved by the Ethics Committee of Ophthalmic Research Center, affiliated to Zahedan University of Medical Sciences, Zahedan, Iran. This study was registered at IRCT.ir with registration number Irct2017041533448n1.

All patients with a diagnosis of CSC and complaining of vision loss in the last three months were included. Patients with other ocular pathologies, significant cardiovascular or thromboembolic history or pregnant females, and cases with a history of previous treatment for CSC, were excluded from the investigation. Diagnosis was performed by a single retina specialist by interpretation of OCT images, demonstrating the neurosensory retinal elevation, and also FAG, presenting the focal leaks at the level of the RPE. The detailed study procedure was explained for all participants and an informed consent letter was obtained from them before any intervention.

All patients underwent a comprehensive ophthalmic examination, including CDVA assessment, using the Snellen visual acuity chart at a distance of 6 m. Slit lamp examination and indirect ophthalmoscopy through dilated pupils by a non-contact 78-diopter lens were performed by an ophthalmologist. In addition, central macular thickness (CMT) was also measured using a Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). All examinations were performed at baseline and also repeated at the four-month follow-up for patients in both intervention and control groups.

Thirty eligible eyes were randomly assigned to the IVB (n = 15) and control (n = 15) groups, so that patients in the intervention group received a single dose of IVB, under

standard conditions, while subjects in the comparison group were followed-up during the same time period without any medical interventions.

In the operating room, a speculum was inserted after prepping and draping and also providing the topical anesthesia. In addition, sterilization of the ocular surface was performed using a solution of povidone iodine 5%. Thereafter, bevacizumab (1.25 mg in 0.05 mL, Avastin®; Roche, Basel, Switzerland) was prepared in a 27-gauge syringe and it was injected, supratemporaly, 4 mm posterior to the limbus. The location was depressed with an applicator and eyes were irrigated using a balanced salt solution (BSS; Plus, Alcon Laboratories, Ft. Worth, TX). All injected patients were recommended to apply the 0.3% ciprofloxacin, six hours per day and 0.1% betamethasone three hours per a day for a duration of 10 days after the IVB injection.

Main Outcome Measure

The mean changes of CDVA and CMT on the fourth month follow-up compared to the baseline values were the primary outcomes. Furthermore, the difference of mean CDVA and CMT on the fourth month follow-up between the two groups were analysed as the secondary outcomes in this study.

Sample Size

To obtain a power of 80% and to detect a difference as large as 0.2 LogMAR between the two groups when the standard deviation (SD) of groups was believed to be 0.19 [13], a sample of 15 in each group was needed. In this calculation, the statistical significance level was assumed to be 0.05.

Randomization

The permuted-block randomization method was used with a random length of block between two and six. The sequence of random allocation was generated by a computer program and concealed from the investigators.

Blinding

The visual examination and OCT measurement were conducted by a trained optometrist, who was masked regarding the randomization and the previous clinical findings. In addition, the biostatistician was blinded to the patients' treatment when statistical analysis was performed on the coded data.

Statistical Analysis

Data were presented with means, SDs, frequencies, and percentages. Baseline characteristics were compared by the Chi-Squared and Fisher's exact test. To evaluate changes within groups, paired sample t-test was used. To compare the groups, independent sample t-test was used. Magnitude of difference was presented by mean difference and its 95% confidence interval. All statistical analysis was performed by the SPSS software (version 24, Armonk, NY: IBM Corp.). All tests were two sided and the significance level was assumed to be 0.05.

Figure 1. Flowchart of the Present Study
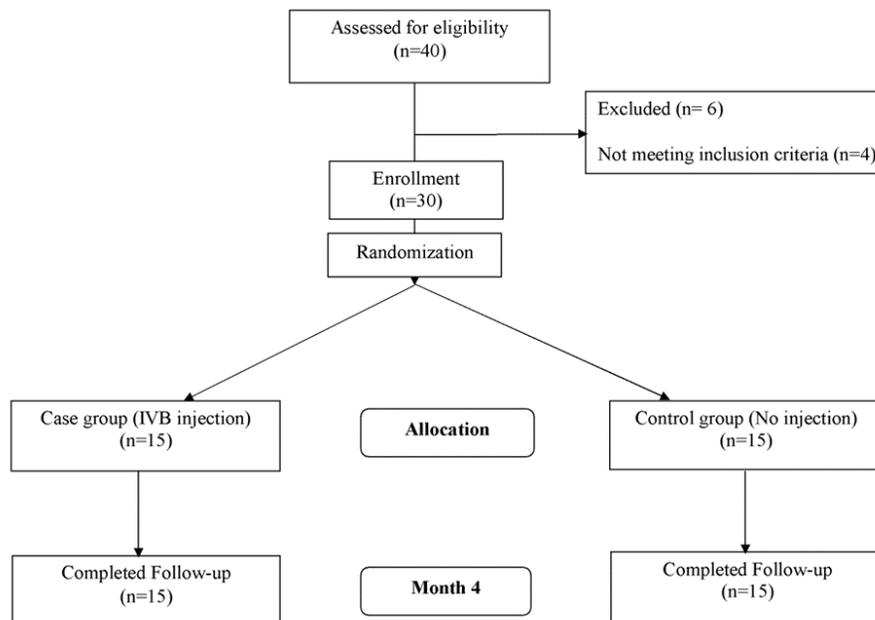
n: number; IVB: Intraviteal Bevacizumab

Table 1. Demographic Characteristics in both Intervention and Comparison Groups

	Total	Intervention Groups	Comparison Groups	P-value
Age (y)	36.9 ± 6.76	37.2 ± 7.32	36.7 ± 6.4	0.833 *
Age Median (range)	36 (23 to 50)	36 (23 to 50)	35 (28 to 50)	
Gender				0.427 †
Male	21 (70.0%)	9 (60.0%)	12 (80.0%)	
Female	9 (30.0%)	6 (40.0%)	3 (20.0%)	

* based on Independent T-test.

† based on Fisher Exact test.

Data in table presented as Mean ± Standard Deviation (SD) or number (%).

Table 2. Corrected Distance Visual Acuity (CDVA) at Baseline and Follow-up on the Fourth Month

	Total	Intervention Group	Comparison Group	Difference	95% CI Lower	95% CI Upper	P-value*
CDVA, baseline (LogMAR)	0.4 ± 0.22	0.39 ± 0.13	0.4 ± 0.28	-0.01 ± 0.08	-0.172	0.16	0.928
CDVA, Month 4 (LogMAR)	0.2 ± 0.2	0.11 ± 0.13	0.29 ± 0.22	-0.18 ± 0.07	-0.32	-0.05	0.009
Changes of CDVA	-0.2 ± 0.21	-0.29 ± 0.18	-0.11 ± 0.21	-0.18 ± 0.07	-0.32	-0.03	0.018
P-value†		< 0.001	0.059				

CDVA: Corrected Distance Visual Acuity; LogMAR: logarithm of the minimum angle of resolution; CI: confidence interval

*Based on independent T-test

† Based on Paired test;

P values less than 0.05 considered significant. Data in table presented as Mean ± Standard Deviation (SD)

Table 3. Central Macular Thickness (CMT) at Baseline and Follow-up of Fourth Month

	Total	Intervention Group	Comparison Group	Difference	95% CI Lower	95% CI Upper	P-value *
CMT, baseline (μm)	396 ± 83	408 ± 91	384± 75	24 ± 30	-39	86	0.442
CMT, month 4 (μm)	300 ± 80	249 ± 42	350 ± 78	-100 ± 23	-147	-53	< 0.001
Changes of CMT	-97 ± 104	-159 ± 98	-35 ± 68	-124 ± 31	-187	-61	< 0.001
P-value †		< 0.001	0.067				

CI: confidence interval, μm: micrometer

* Based on independent T-test

† Based on Paired test.

P values less than 0.05 considered significant. Data in table presented as Mean ± Standard Deviation (SD)

RESULTS

In this pilot RCT, a total of 30 eligible patients (male, 70%) with a clinical diagnosis of CSC and a mean ± SD age of 36.93±6.76 years were included. All enrolled patients completed their follow-up examination and there was no patient that refused to continue participation, as shown in Figure 1.

Demographic characteristics of patients in both intervention and control groups are presented in Table 1. As indicated, there was no statistically significant difference between intervention and control groups in terms of age and gender.

Mean CDVA at both time points of baseline and fourth month follow-up are summarized in Table 2. The mean baseline CDVA was 0.39 ± 0.13 LogMAR in the intervention group, which was improved to 0.11 ± 0.13 LogMAR on the fourth month (P < 0.001), while this improvement was not observed in the control group (P = 0.059). In addition, it is obvious that higher mean CDVA (P = 0.009) and more significant improvement (P = 0.018) were detected in the intervention group compared with the control group. However, this difference was a bit lower than the clinical significant threshold (0.18 versus 0.20).

Regarding the analysis of CMT (Table 3), the current findings were in line with CDVA outcomes, which showed

significant reduction of CMT only in the IVB group (P < 0.001) and also thinner CMT in cases, who were injected by IVB compared to patients without any injection at the fourth month follow-up (249 ± 42 μm versus 350 ± 78 μm, P < 0.001). In addition, more reduction of CMT occurred in the intervention group compared to the control group (159 ± 98 μm versus 35 ± 68 μm, P < 0.001). Furthermore, no ocular complication, including extensive haemorrhage, increase of Intraocular Pressure (IOP), and ocular inflammation was observed during and/or after the injection.

DISCUSSION

The physiopathology of CSC has yet to be fully understood and it is believed that multiple causes and mechanisms are found in such patients, which eventually lead to hyperdynamic choroidal circulation and choroidal vascular hyperpermeability [21]. In these patients, breakdown of RPE barriers occurs due to increased hydrostatic choroidal pressure, which causes subsequent leakage of the fluid in the sub-retinal space [22]. Furthermore, CSC has been taken in consideration in the past few years by investigations of different treatment modalities for these patients, however, a clear scheme has not been fully elucidated [23].

Although the efficacy and favorable visual outcomes of Photodynamic Therapy (PDT) have been shown in the treatment of patients with CSC, it can also be associated with complications, including foveal thinning, RPE atrophy, choriocapillaris ischemia, Choroidal Neovascularization (CNV), and transient abnormal response on multifocal Electroretinography (mfERG) [24]. In addition, less accessibility and high expenses of PDT can be considered as other limitations of PDT therapy for patients with CSC [25]. Furthermore, greater safety and efficacy of IVB have been shown compared with PDT therapy [26].

Furthermore, historical thermal (argon) laser photocoagulation is another proposed therapeutic modality for patients with CSC, which may accelerate the resolution of the associated neurosensory detachment [8]. Based on the literature, significant adverse effects, including permanent scotoma, enlargement of RPE scar, secondary laser-induced CNV formation, and inadvertent foveal photocoagulation may occur [13, 27]. In addition, Subthreshold Diode Laser Micropulse (SDM) photocoagulation is another suggestion, the safety and efficacy of which has been reported in the management of patients with CSC and the superiority of SDM was detected compared with IVB in the study of Koss et al. [28].

Based on the literature, it has been demonstrated that the Vascular Endothelial Growth Factor (VEGF) level in aqueous humour of patients with CSC is higher compared to the normal population [29]. In this regard, other studies have concluded that VEGF may contribute to the pathogenesis of CSC and also be involved in fluid leakage in these patients, therefore, intravitreal anti-VEGF therapy has been studied by various research groups [13-16, 19, 20, 26, 30, 31]. The current researchers believe that VEGF can be considered as a "vascular permeability factor" and bevacizumab may reduce choroidal hyperpermeability due to the reduction of VEGF level and reverse choroidal changes due to its anti-permeability properties.

In this pilot RCT, the therapeutic effect of IVB was investigated on both functional and anatomical characteristics of patients with CSC. This research determined that CDVA was improved significantly in the intervention group, while it was not observed in the control group. Greater improvement of CDVA was detected in the IVB group compared to patients in the control group. However, this difference was a bit lower than the clinical significant threshold (0.18 versus 0.20). In addition, CMT findings were in line with CDVA changes in both groups, revealing the significant reduction of CMT only in the intervention group. Also, thinner central retina was found in the intervention group compared to patients, who were in the control group at the fourth month follow-up.

Although the safety and efficacy as well as both anatomical and functional benefits of IVB in the treatment of CSC have been shown in different case series [13, 30, 31], these findings need to be validated further by a RCT with consideration of a comparison group. Recent studies were mostly uncontrolled prospective case series and were conducted on a small sample size. In addition, Park et al. [20] did not find any difference between cases injected by IVB and those, who were only followed-up without any treatment; they found that IVB injection could accelerate the spontaneous absorption of sub-retinal fluid and decrease the probability of the degeneration of the photoreceptor cells.

On the other hand, a lack of positive effect of IVB on CSC patients was reported in a meta-analysis by Chung et al. [19], which could be attributed to the clinical heterogeneity of the selected four comparative studies. One of the reasons for heterogeneity of this study is the consideration of both acute and chronic CSC eyes, which may show different responses to treatment. Usage of different concentrations of bevacizumab and lack of a

unique control group could be considered as other heterogeneity factors. In addition, lack of significant effectiveness of IVB on patients with CSC could be attributed to the study design and/or small number of cases in the study by Lim et al. [32].

Akhlaghi et al. [33] did not find the effectiveness of IVB on CSC patients in the short term follow-up of three months, while Semeraro et al. [34] found it as an effective treatment in longer follow-up of nine months. All the patients in both intervention and control groups were followed up for four months due to the fact that foveal photoreceptor atrophy in patients with CSC might occur up to four months after the onset of symptoms [35]. Also, the spontaneous treatment of CSC in a duration of three months has been reported [8], therefore, it was not ethical to follow-up the subjects in the control group without any intervention for a longer time.

CONCLUSION

Although bevacizumab seems to be effective in improvement of both anatomical and functional visual outcomes in patients with CSC, more investigations with a larger sample size and longer follow-up are recommended in order to overcome the possible limitations of the current clinical trial.

DISCLOSURE

Ethical issues have been completely observed by the authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given their final approval for the version to be published. No conflict of interest has been presented.

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