Original Research Paper
Role of Intravitreal Bevacizumab for the Treatment of Acute Central Serous Chorioretinopathy

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Abstract
Purpose: To find out the role of intravitreal bevacizumab in the treatment of acute central serous chorioretinopathy (CSC).

Methods: A total of 24 patients of CSC were included in this study and were divided into two groups with 12 patients each. Treatment group received a single intravitreal injection of bevacizumab (1.25mg/0.05ml; Avastin) and in other group no treatment was given and served as control group. Central macular thickness (CMT) and best corrected visual acuity (BCVA) were measured at baseline, 6 weeks, 10 weeks, 18 weeks and 24 weeks and were compared between treatment and control groups.

Results: Mean CMT in treatment group at baseline was 507.92±81.37µ (range: 380-630µ) which improved to 392.17±65.63µ (p value-0.000) at 6 weeks; 344.67±59.93µ (p value-0.000) at 12 weeks; 296.83±39.93µ (p value-0.000) at 18 weeks and 269.75±30.85µ (p value-0.000) at 24 weeks after injection. Baseline BCVA in treatment group was 0.58 log MAR units which improved to 0.44 log MAR (p value-0.000) at 6 weeks; 0.33 log MAR (p value-0.000) at 12 weeks; 0.26 log MAR (p value-0.000) at 18 weeks and 0.12 log MAR (p value-0.000) at 24 weeks after injection. Mean CMT in control group at baseline was 505.92±123.78µ (Range: 310-670µ) which improved to 398.67±79.23µ (p value-0.000) at 6 weeks; 360.42±73.37µ (p value-0.000) at 12 weeks; 324.67±56.36µ (p value-0.000) at 18 weeks and 293.83±83µ (p value-0.000) at 24 weeks after injection. Mean baseline BCVA in control group was 0.57 log MAR units which improved to 0.47 log MAR (p value-0.000) at 6 weeks; 0.37 log MAR (p value-0.000) at 12 weeks; 0.27 log MAR (p value-0.000) at 18 weeks and 0.175 log MAR (p value 0.000) at 24 weeks after injection. On comparison of CMT and BCVA at baseline and different follow-ups, between the two groups, no statistically significant difference was seen.

Conclusion: In this study we found that there was no benefit of intravitreal bevacizumab over observation in the management of acute CSC.

Keywords: central serous chorioretinopathy (CSC), best corrected visual acuity (BCVA), central macular thickness (CMT), photodynamic therapy (PDT), optical coherence tomography (OCT), fundus fluorescein angiography (FFA).

Introduction
Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina and frequently causes mild to moderate visual impairment. Fortunately, the disorder is self-limited in the majority of patients, who also regain excellent vision. Although the prognosis is usually favorable, some patients who do not have spontaneous resolution develop pigment epithelial and photoreceptor damage with
visual impairment. The mechanism for the development of CSC remains unclear. According to one of the hypothesized mechanisms, abnormalities in choroidal perfusion can be causative factors in CSC. Recent indocyanine green angiography in patients with CSC has demonstrated evidence of choroidal lobular ischemia and choroidal venous congestion and also revealed multiple areas of choroidal vascular hyperpermeability in intermediate stages of the study. The cause of the venous congestion has not been determined, but it may be a response to ischemia and delayed arterial filling or a consequence of outflow obstruction. Choroidal hyperpermeability at foci of subretinal fluorescein leakage is a frequent finding but choroidal hyperpermeability can also be found without associated fluorescein leakage suggesting more generalized retinal pigment epithelium (RPE) or choroidal vascular disturbance. Vascular endothelial growth factor (VEGF) is produced by damaged retinal and choroidal cells when abnormal vascular perfusion causes ischemia. By uncoupling endothelial cell-to-cell junctions, VEGF causes vascular permeability and edema. CSC may begin with the changes in choroidal permeability. Therefore bevacizumab may be utilized as a treatment to reduce the choroidal hyperpermeability and reverse the changes seen in CSC. Recently there has been a case report suggesting that intravitreal application of bevacizumab, a humanized monoclonal antibody to VEGF, may have beneficial effects in chronic CSC. However, we used intravitreal bevacizumab injection for treatment in a few cases of acute CSC. The purpose of the present study is to report the use of intravitreal bevacizumab injection as a treatment for patients with acute CSC.

Methodology
This is a prospective study conducted at a tertiary care eye facility in northern India. Institutional ethical committee clearance was obtained as well as patient written consent. A total of 24 patients of acute CSC were included in this study. Diagnosis was made on the basis of history, dilated fundus examination, fundus fluorescein angiography and spectral domain- optical coherence tomography. We divided the patients into two groups with 12 patients each. Treatment group received a single intravitreal injection of bevacizumab (1.25mg/0.05ml; Avastin) and in other group no treatment was given and served as control group. Central macular thickness (CMT) using spectral domain optical coherence tomography and best corrected visual acuity (BCVA) were measured at baseline, 6 weeks, 10 weeks, 18 weeks and 24 weeks and were compared between treatment and control group. All patients were informed about other therapeutic options and the off-label situation of this therapy. Treatment was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and the informed patient’s consent.

Results
Age range in control group was 28-52 years with mean age of 39.0±6.86 years whereas age range in avastin group was 26-49 years with a mean age of 37.08±6.45 years. There were 8 males and 4 females in control group; 7 males and 5 females in avastin group.

In the control group Baseline mean BCVA (table-1) was 0.57 logMAR units which improved to 0.47 at 6 weeks; 0.37 at 12 weeks; 0.27 at 18 weeks; and 0.175 at 24 weeks. Mean central macular thickness (CMT) in the control group (table-2) at baseline was 505.92±123.78μm (range 310-670μm) which improved to 398.67±79.23 at 6 weeks; 360.42±73.37 at 12 weeks; 324.67±56.36 at 18 weeks; and 293.83±40.65 at 24 weeks.

In Avastin group Baseline mean BCVA (table-3) was 0.58 logMAR units which improved to 0.44 at 6 weeks; 0.37 at 12 weeks; 0.27 at 18 weeks; and 0.12 at 24 weeks. Mean central macular thickness (CMT) in the control group (table-2) at baseline was 505.92±123.78μm (range 310-670μm) which improved to 398.67±79.23 at 6 weeks; 360.42±73.37 at 12 weeks; 324.67±56.36 at 18 weeks; and 293.83±40.65 at 24 weeks.

In Avastin group Baseline mean BCVA (table-3) was 0.58 logMAR units which improved to 0.44 at 6 weeks; 0.33 at 12 weeks; 0.26 at 18 weeks; and 0.12 at 24 weeks. Mean central macular thickness (CMT) in the control group (table-4) at baseline was 507.92±81.37μm (range 380-630 μm) which improved to 392.17±65.63 at 6 weeks;
344.67±59.93 at 12 weeks; 296.83±39.93 at 18 weeks; and 269.75±30.85 at 24 weeks.

On comparison of CMT between the two groups (Table 5) the p-value at 6, 12, 18 and 24 weeks came out to be 0.827, 0.564, 0.163 and 0.102 respectively which was not statistically significant. On comparison of BCVA between the two groups (Table 6) the p-values at 6, 12, 18 and 24 weeks came out to be 0.770, 0.634, 0.909 and 0.235 respectively, which was again not statistically significant.

Table 1: BCVA in control group

|          | Mean BCVA (logMAR) | T-stat | p-value |
|----------|-------------------|--------|---------|
| Baseline | 0.57              |        |         |
| 6 weeks  | 0.47              | 4.06   | 0.001   |
| 12 weeks | 0.37              | 5.42   | 0.000   |
| 18 weeks | 0.27              | 10.90  | 0.000   |
| 24 weeks | 0.175             | 11.65  | 0.000   |

Table 2: CMT in control group

|          | CMT (μm) range   | Mean CMT (μm) | T-stat | p-value |
|----------|------------------|---------------|--------|---------|
| Baseline | 310-670          | 505.92±123.78 |        |         |
| 6 weeks  | 270-510          | 398.67±79.23  | 7.15   | 0.000   |
| 12 weeks | 240-475          | 360.42±73.37  | 8.03   | 0.000   |
| 18 weeks | 235-410          | 324.67±56.36  | 8.52   | 0.000   |
| 24 weeks | 230-355          | 293.83±40.65  | 8.42   | 0.000   |

Table 3: BCVA in Avastin group

|          | Mean BCVA (logMAR) | T-stat | p-value |
|----------|-------------------|--------|---------|
| Baseline | 0.58              |        |         |
| 6 weeks  | 0.44              | 7.34   | 0.000   |
| 12 weeks | 0.33              | 8.66   | 0.000   |
| 18 weeks | 0.26              | 11.66  | 0.000   |
| 24 weeks | 0.12              | 10.01  | 0.000   |

Table 4: CMT in Avastin group

|          | CMT (μm) range   | Mean CMT (μm) | T-stat | p-value |
|----------|------------------|---------------|--------|---------|
| Baseline | 380-630          | 507.92±81.37  |        |         |
| 6 weeks  | 290-505          | 392.17±65.63  | 10.88  | 0.000   |
| 12 weeks | 255-465          | 344.67±59.93  | 21.65  | 0.000   |
| 18 weeks | 235-370          | 296.83±39.93  | 12.34  | 0.000   |
| 24 weeks | 232-310          | 269.75±30.85  | 13.58  | 0.000   |

Table 5: Comparison of BCVA between the two groups

|          | Mean BCVA control group (logMAR) | Mean BCVA avastin group (logMAR) | z-stat | p-value |
|----------|----------------------------------|----------------------------------|--------|---------|
| Baseline | 0.57                             | 0.58                             | 0.18   | 0.855   |
| 6 weeks  | 0.47                             | 0.44                             | -0.29  | 0.770   |
| 12 weeks | 0.37                             | 0.33                             | -0.47  | 0.634   |
| 18 weeks | 0.27                             | 0.26                             | -0.11  | 0.909   |
| 24 weeks | 0.175                            | 0.12                             | -1.18  | 0.235   |

Table 6 Comparison of CMT between the two groups

|          | Mean CMT (μm) control group       | Mean CMT (μm) avastin group      | z-stat | p-value |
|----------|----------------------------------|---------------------------------|--------|---------|
| Baseline | 505.92±123.78                    | 507.92±81.37                    | 0.046  | 0.962   |
| 6 weeks  | 398.67±79.23                     | 392.17±65.63                    | -0.22  | 0.827   |
| 12 weeks | 360.42±73.37                     | 344.67±59.93                    | -0.57  | 0.564   |
| 18 weeks | 324.67±56.36                     | 296.83±39.93                    | -1.39  | 0.163   |
| 24 weeks | 293.83±40.65                     | 269.75±30.85                    | -1.63  | 0.102   |
Discussion
CSC is a disease of the retina characterized by serous detachment of the neurosensory retina secondary to one or more focal lesions of the RPE. The high spontaneous remission rate favors conservative management as a first line therapeutic option. But there is some evidence supporting the benefit of early treatment for CSC. A potential benefit for early resolution may be mediated by a lower rate of RPE degeneration in the treated eye which is also warranted because of an uncertain relation between the onset of detachment and that of symptoms and special occupational demands for binocular visual function.

Although there is no definite evidence about early treatment for CSC, many retinal specialists tend to consider laser photocoagulation, photodynamic therapy (PDT) with verteporfin and some medical treatment as early treatment. Laser photocoagulation and PDT with verteporfin accelerate the resolution of detachment, but they should be used with caution because they can induce permanent damage to the RPE or choriocapillary, severe retinal thermal injury, subretinal choroidal neovascularization, often many years after the primary incident. One experimental study showed that PDT with verteporfin resulted in morphological and functional breakdown of the outer blood-retinal barrier and function of RPE or RPE cells themselves with increasing concentration of verteporfin.

In this small case series, we demonstrated that there was resolution of subretinal fluid and improvement in BCVA in both groups over a period of six months. There are number of short case series in past who claim that intravitreal injection of bevacizumab accelerate the resolution of subretinal fluid and improvement of BCVA in CSC patients. But the shortcoming of these few case series is that they have not compared the treatment group with that of the controls. As we know that CSC is a self resolving condition, so we cannot conclude whether the improvement in BCVA and subretinal fluid in these patients was because of bevacizumab or was it because of natural history of this condition.

To know the actual effect of intravitreal bevacizumab in these patients, it is important to compare it with controls. We compared the two groups in this case series, and found that in both the groups the subretinal fluid resolved and BCVA improved regardless the treatment received or not. When we compared the BCVA and CMT at various follow-ups between the two groups, we did not found any statistically significant difference between the two groups. Based on these findings we found no treatment benefit over conservative management in these patients.

The strength of this study is that we have taken a control group, so that we can actually know if there is any benefit of this treatment modality over observation in these patients. The limitation of this study is that we have taken small sample size, which is not sufficient to make a solid conclusion.

Conclusion
Based on this case series we found no benefit of intravitreal bevacizumab over observation in acute CSC. In future large sample size with control group is warranted before any conclusion can be made.

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