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Original Research Article

Micropulse diode laser versus bevacizumab in chronic central serous chorioretinopathy: a pilot study

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ABSTRACT

Background: Central serous chorioretinopathy (CSC) is an idiopathic condition with an illdefined aetiopathogenesis and no clearly effective treatment. The choice of treatment include thermal laser photocoagulation, photodynamic therapy (PDT), subthreshold micropulse laser and anti VEGF.
Methods: In a prospective nonrandomized pilot trial we evaluated two of these modalities subthreshold micropulse laser treatment and intravitreal anti VEGF in 20 consecutive cases of non-resolving CSC of duration 3 to 6 months with vision below 6/12 treated with either Bevacizumab for leakage close to fovea or subthreshold micropulse 810 diode laser for extrafoveal leakage (10% duty cycle, 100 µ spot size) as seen on fluorescein angiography.
Results: At 6 months follow up complete resolution was seen in 9/10 in laser and 6/10 in Avastin group. The mean visual acuity improved from Log MAR 0.61 ± 0.17 at baseline to Log MAR 0.07± 0.11 post treatment in laser group and from Log MAR 0.59 ± 0.17 to Log MAR 0.18 ± 0.09 in the Avastin group . Similarly mean central macular thickness decreased from 607 µ ± 162.1 to 206 µ ± 55 in laser group and from 601 µ ± 182 to 262 µ ± 75 in those receiving Avastin. Both visual outcome and resolution of serous detachment was better with Micropulse laser as compared to Bevacizumab.
Conclusions: Micropulse diode laser treatment of CSC has higher rate of resolution and better visual outcome as compared to Bevacizumab injections.

Keywords: Chronic central serous chorioretinopathy, Micropulse diode laser, Bevacizumab

INTRODUCTION

Central serous chorioretinopathy (CSC) is an idiopathic disorder characterized by sensory neural detachment most commonly involving the macula.[1] Though spontaneous resolution is the norm in most patients, chronic disease in a subset of patients can result in significant visual morbidity. This chronic variety has been shown to have more widespread RPE abnormalities, termed as diffuse pigment epitheliopathy and is considered to be a distinct subtype.[2] Acute or classic CSC may be managed by observation alone whereas in chronic cases with deterioration of vision, various treatment options have been explored.[3] Thermal laser photocoagulation to site of fluorescein leak has been found to hasten the recovery but it does not alter the final visual outcome.[4,5] Laser scar induced scotomas and risk of secondary choroidal neovascular membranes (CNVM) are the problems associated with thermal laser. Treatment with half fluence photodynamic therapy (PDT) is perhaps the most promising among the various treatment options, in terms of resolution of fluid and improvement of vision.[6] However, complications such as retinal pigment atrophy, choroidal ischemia and secondary CNVM have been reported with PDT as well. The recurrent cost of Verteporfin dye for PDT puts it out of reach of most

patients in developing nations such as India. Two other modalities which are have been reported to be safe, efficacious and more cost effective in treating chronic CSC are micropulse laser photocoagulation and Bevacizumab (Avastin) injection.[7,8] Both these modalities are relatively safe and cost effective treatment options in cases of CSC, which fail to resolve with observation alone. Studies comparing these two modalities are lacking and hence a pilot study was conducted to compare sub-threshold micropulse diode laser with intra-vitreal Bevacizumab for the treatment of chronic CSC.

METHODS

This was a prospective open label nonrandomized comparative study done at a tertiary care hospital. Institutional ethical clearance was taken and guidelines of the Helsinki convention were followed. The subjects were drawn from the patients reporting for retina consultation at the retina OPD. All cases underwent full ophthalmic examination including optical coherence tomography (OCT) and fundus fluorescein at baseline before inclusion. Only cases showing serous sensory retinal detachment on OCT with typical pattern of dye leakage on FFA and failure to resolve after documented 3 months of observation and follow up from onset with associated vision drop from baseline by at least 5 ETDRS letters were considered for treatment and included in the study. Failure to resolve was defined as less than 100 µ decrease in central macular thickness (CMT) from baseline on OCT after 3 months of regular follow up. Excluded from the study were cases with any other coexistent retinopathy/uveitis, previously treated cases, use of steroids in any form in last 6 months, intraocular surgery in last 3 months and disc abnormalities such as optic disc pit. Those with leakage within 300 µ of the foveal centre were given Intravitreal Bevacizumab whereas those with leakage more than 300 µ from foveal centre received micropulse diode laser. Micropulse diode laser was done in one sitting with 10% duty cycle, 100 µ spot size and 0.2 sec time. Power used was 40% of the titrated power at 10% duty cycle which produced just visible burns outside the macula. Intravitreal Bevacizumab Injection 1.25 mg in 0.05 ml was given in the operation theatre under sterile precautions. Off label consent for Bevacizumab injection was taken from all patients. Injection was repeated monthly if required in case of inadequate response at a gap of minimum one month upto a maximum of three injections. Inadequate response was defined as persistence of subretinal fluid with less than 100 µ decrease in CMT. Patients were followed up at monthly intervals and at each follow up full ophthalmic examination including best corrected visual acuity by ETDRS chart and OCT. FFA was also carried out at the final follow up, to document absence of leakage, Results were compared at 6 months from start of treatment. The treatment groups were compared in terms of proportion showing complete resolution, visual outcome and decrease in central macular thickness and subfoveal fluid. Complete resolution or cure was defined as absence of submacular fluid at the end of 6 months of follow up after start of treatment. Stastical analysis was done using SPSS version 20. Paired T test was used for comparison within the groups and unpaired T test for inter group comparison. P value of less than 0.05 was taken as significant and 95% confidence limit (CI) was calculated for the difference in means.

RESULTS

A total of 20 patients were included in the study 10 in each group. The comparison of baseline characteristics between the two groups show that they were well matched for the base line parameters (Table 1). The average age of subjects was around 41 years and pretreatment vision was in the range of Log MAR 0.4 to 0.9 (Converted Snellens equivalent: 6/15 to 6/48).

Table 1: Baseline characterstics of the study sample population.

	Gp 1 MPDL (n= 10)	Gp2 Bevacizumab (n=10)	Significance
Age*	43.4 ± 5.23; 36 - 52	41.3 ± 5.12; 30- 50	p=0.56
Gender M/F	8(80%)/2(20%)	7(70%)/3(30%)	p=0.61
Initial Vision Log MAR*	0.61 ± 0.17; 0.4 – 0.9	0.59 ± 0.17; 0.4-0.9	p= 1
Baseline CMT*	607µ ± 162.16; 380 - 840 µ	601 µ ± 182.28; 384- 830 µ	p=0.88

* Mean ± SD & Range

The treatment results for each group in terms of visual gain, reduction of central macular thickness are listed in Table 2. Both the groups showed statistically significant treatment response with decrease in serous macular detachment measured as reduction in central macular thickness ($p < 0.05$) and fluid levels. This resulted in statistically significant improvement in vision in both the groups ($p < 0.05$). Comparing the treatment response between the two modalities (Table 2 and 3) it is seen that gain in vision was more in the group that received treatment with micropulse diode laser photocoagulation and this difference was statistically significant ($p < 0.05$) (Table 3). The resolution of serous detachment when measured as mean of the decrease in central macular thickness in both groups was similar with no statistically significant difference ($p = 0.239$, Table 3). However when complete resolution or cure rate was compared complete resolution or cure was seen in 9 of 10 patient (90%) in MPDL group and 6 of 10 patients (60%) in Bevacizumab group (Figure 3). Those with incomplete resolution had shallow sub macular fluid with evidence of active leakage on angiography. In the Bevacizumab

group average number of injections was 2.2 with 6 patients receiving a maximum of three injections.

Table 2: Showing treatment outcome for vision and macular thickness before and after treatment within each group.

Group 1(Micro pulse laser)	Mean	Std Deviation	Range
Base line Vision in Log MAR	0.61	0.17	0.4 – 0.9
Post Treatment Final Vision Log MAR	0.07	0.11	- 0.08 – 0.28
Gain in Vision Initial Vs Final	0.538	0.133	95 % CI : 0.443 – 0.633
Significance Initial Vs Final Vision	p = 0.000 (significant)		
Base line CMT* in µ	607.0	162.1	380 -840
Final CMT* in µ post treatment	206.4	55.3	130 - 300
Reduction in Thickness Initial Vs Final	400.6	112.0	95 % CI : 320.5 - 480.7
Statistical Significance Initial Vs Final CMT	p= 0.0000 (significant)		
Baseline Mean fluid level in µ	280	67.7	160 - 420
Final Mean fluid level in µ	27	88.3	0 - 270
Significance Initial Vs Final	P<0.0001		
Group 2 (Bevacizumab)			
Base line Vision in Log MAR	0.59	0.17	0.4 - 0.9
Final Vision Log MAR post treatment	0.18	0.09	- 0.02 – 0.3
Gain in Vision Initial Vs Final	0.414	0.121	95% CI : 0.327 – 0.501
Statistical Significance Initial Vs Final Vision	p= 0.000 (significant)		
Base line CMT* in µ	600.9	182.3	384 - 830
Final CMT* in µ post treatment	262	74.8	155 - 360
Reduction in Thickness Initial Vs Final	338.9	114.4	95% CI : 257.0 – 420.8
Statistical Significance Initial Vs Final CMT	p = 0.000 (significant)		
Baseline Mean fluid level in µ	299	76.9	200- 410
Final Mean fluid level in µ	85.71	148.2	0 - 340
Significance Initial Vs. Final	P=0.0006		

Table 3: Comparison of treatment outcome between the two groups Gp 1 Micropulse diode laser versus Bevacizumab.

	Post treatment gain in vision (Log MAR) Mean difference & 95 % CI	Decrease in central macular thickness (CMT in µ) Mean Difference & 95 % CI	Proportion with active leakage on FFA	Decrease in Fluid level in µ, Mean Difference & 95 % CI
Gp1 Versus Gp 2	0.158; (0.034-0.282)	61; (-44.7 – 168.1)	Gp 1 :1/10(10 %) Gp 2 : 4/10(40 %)	65.2; (-140.5 – 10.1)
Significance	p= 0.016 (significant)	p= 0.239 (not significant)	p= 0.13(not significant	p=0.0854 (not significant

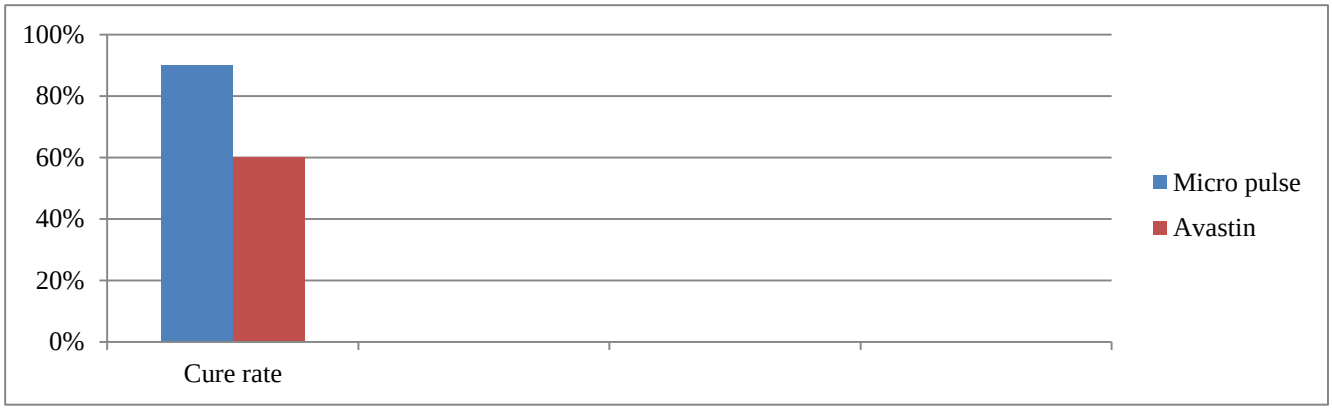

Figure 1: Rate of complete resolution between the two groups.

DISCUSSION

The treatment of CSC which does not resolve spontaneously by three months continues to be a matter of debate with several options available but none of them perfect. Intervention after a period of 3 months of observation for lesions with active leakage and subretinal fluid may be considered to hasten recovery and prevent permanent vision loss.[9] The various interventions that have been described are: thermal laser photocoagulation to active leakage area, PDT, sub threshold laser and intravitreal anti VEGF.[10] Thermal laser phocoagulation is the oldest but it has the disadvantage of causing visible scar which can cause collateral damage and predispose to choroidal neovascularisation.[11] PDT has been found effective in various studies but it also can cause retinal pigment epithelium (RPE) damage, choroidal ischemia and scotoma.[12] Sub threshold micropulse laser has been shown to achieve resolution without any visible damage which is a major advantage apart from simplicity of the procedure and less cost as compared to PDT.[13] Anti VEGF (Bevacizumab) helps in faster resolution of subretinal fluid with restoration of normal anatomy which may promote RPE healing.[14] In this comparative study both subthreshold micropulse diode laser and injection Bevacizumab were found to aid resolution of the serous detachment with improvement of vision which was statistically significant when compared to baseline values. Micropulse diode appears to give a superior outcome as compared to Bevacizumab which was statistically significant for gain in vision. Complete resolution was achieved in all but one case treated with micropulse whereas 4 patients in the Bevacizumab group had shallow macular detachment at the time of final analysis which accounted for the poorer gain in vision in this group. No visible scarring was seen with the subthreshold diode laser. Reports on the efficacy of Bevacizumab have been equivocal and controversial. Artunay and colleagues in a prospective open labeled non randomized trial comprising of 30 eyes with chronic symptomatic CSC reported significant improvement with single injection Bevacizumab.[15] In a retrospective analysis Kim et al noted that good responders to Avastin had smaller lesions and thicker choroids.[16] However Liu et al in a meta- analysis and review concluded that there was insufficient evidence for the superiority of Bevacizumab over other modalities.[17] In our study, though treatment with Bevacizumab resulted in significant overall improvement, but 4 out of 10 cases failed to resolve fully during this short period of follow up. Bevacizumab therefore may be effective as an adjunct to reduce the subretinal fluid but its role as a primary therapy is debatable. The mechanism of action of subthreshold diode laser is as yet unclear but it is postulated to elicit a non thermal biological response causing a resetting of the RPE pump and down regulation of various permeability factors.[18,19] A number of previous studies have reported efficacy of micropulse Dioode laser photocoagulation for treatment of CSC but only a few of them are comparative clinical trials, the majority being retrospective and prospective case series.[20-22] Koss MJ and others in their comparative study of subthreshold diode laser treatment versus Bevacizumab reported superior results with diode laser in the treatment of non resolving CSC but they did not have a defined protocol for bevacizumab reinjection and laser was repeated in some cases.[23] We had a well defined criteria for reinjection and all patients received laser treatment only once but still the eventual outcome was better for the laser group. One of the problems of treating with subthreshold micropulse is the calculation or titration of the dose of energy to be set for laser since there is no visible end points. This has been done in two different ways in previous studies. In one technique the power is titrated to get a just visible burn away from the macula using a fixed spot size and duration in the continuous wave mode, and then the same power or double the power is used in micropulse mode with 10 to 15% duty cycle.[24] The other method is to titrate in the micropulse mode to get a just visible burn and then use 10 to 40% of the titrated power for treatment.[25] Both techniques have been found efficacious and energies upto 1.5 to 2 Watts have been found safe and non scarring when used in 5 to 15 % duty cycles. However the minimum energy which is effective in most eye is still not well defined. In this study we have titrated the burn in the micropulse mode and finally used 40% of the titrated power. No visible scar was seen even after 6 months of follow up and treatment efficacy indicates that the required energy could be delivered at the RPE level without clinically visible damage.

CONCLUSION

To conclude, subthreshold micropulse laser photocoagulation to area of active leak appears to be a safe and effective modality to treat non resolving CSC. The outcome was superior in terms of visual recovery and complete resolution of subretinal fluid as compared to Bevacizumab. Injection Bevacizumab may be useful as an adjunct rather than for primary therapy. The prospective data and well defined treatment protocols for each arm were the strengths of the study. The small sample size, lack of randomization, a slightly different criteria for selection of patients in each arm and the lack of long term follow up were some of the limitations of the study.

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