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Research Article

Comparison of Oral Carbonic Anhydrase Inhibitor with Topical Carbonic Anhydrase Inhibitor in Central Serous Chorioretinopathy

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ABSTRACT

Background: Central serous chorioretinopathy (CSC) is a disorder of the retina that causes a collection of fluid under the retina, which affects vision. The use of carbonic anhydrase inhibitors to improve the function of the pump in the retinal pigment epithelium and to promote fluid reabsorption. Comparative evidence comparing oral and topical formulation is however limited.

Objective: To compare the efficacy and safety of oral acetazolamide versus topical dorzolamide in the management of CSC.

Study Design: The study was prospective, randomized and comparative in a tertiary care ophthalmology department.

Methods: The study was conducted over a 12-month period, which involved 100 patients with the diagnosis of CSC. Patients were divided into two groups: one that received oral acetazolamide, 250 mg twice daily; and a second that received topical dorzolamide, 2% eye drops, three times a day, for 8 weeks. The outcomes measured were the changes in best corrected visual acuity (BCVA), central macular thickness (CMT), resolution of subretinal fluid (SRF), and adverse effects. Appropriate statistical tests were used and $p < 0.05$ was taken to be significant.

Results: A significant improvement in BCVA and a decrease in CMT ($p<0.001$) was observed in both treatment groups. Compared to the topical dorzolamide group, the oral acetazolamide group showed significant improvements in BCVA (0.31 ± 0.10 vs 0.24 ± 0.09 logMAR), more deep retinal layers thinning with CMT (146 ± 42 μm vs 116 ± 37 μm), and a higher proportion of complete SRF resolution (78% vs 60%). But the oral group had more systemic complaints (paresthesias, gastrointestinal upset), while the topical group had more eye complaints.

Conclusion: Oral acetazolamide is more effective than topical dorzolamide in both anatomical and functional results in the treatment of CSC; however oral acetazolamide has greater systemic side effects. Dorzolamide can be used topically in some patients as an alternate therapy.

Keywords: Central Serous Chorioretinopathy, Acetazolamide, Dorzolamide, Carbonic Anhydrase Inhibitors, Subretinal Fluid, Optical Coherence Tomography.

INTRODUCTION

Central Serous Chorioretinopathy (CSC) is a condition of the retina that involves fluid building up under the neurosensory retina from a breakdown in the function of the retinal pigment epithelium (RPE) and increased permeability of the choroid [1, 2]. Most commonly seen in young and middle-aged adults, especially in males aged 20–50 years. Patients often have symptoms of blurred vision, metamorphopsia, micropsia, decreased contrast sensitivity, and central scotoma that may seriously disrupt their daily lives and quality of life [3].

The exact mechanism of the development of CSC has not been fully explained, but there

have been many factors found to increase risk of developing it, such as psychological stress, using steroids, high blood pressure, pregnancy, sleep disturbances, and type-A personalities [4]. New imaging technologies, especially optical coherence tomography (OCT) and fluorescein angiography, have helped researchers better understand how the disease works and the earlier detection and monitoring of treatments [5].

Acute CSC can be self-limiting, and may resolve spontaneously within three to four months. Long-lasting or recurring cases, however, may lead to more permanent changes in the retina, specifically the retinal pigment epithelium, damage to the photoreceptor cells and permanent loss of vision [6]. A number of treatment options have thus been evaluated to expedite resolution of subretinal fluid and the recovery of visual acuity. They consist of laser photocoagulation, anti-vascular endothelial growth factor (anti-VEGF) drugs, mineralocorticoid receptor antagonists, and carbonic anhydrase inhibitors [7, 8].

The use of carbonic anhydrase inhibitors has been highlighted in relation to their capacity to facilitate fluid flux across the retinal pigment epithelium into the subretinal space, to facilitate the uptake of subretinal fluid [9]. Systemic CAI (Oral acetazolamide) has been found to be effective in resolving fluid faster and improving retinal architecture in CSC patients [10]. In a study by Pikkel et al., the patients receiving oral acetazolamide demonstrated faster subjective visual improvement and earlier resolution of subretinal fluid than those not treated with oral acetazolamide. Systemic reactions, though, may include paresthesia, fatigue, gastrointestinal side effects and metabolic changes that restrict its use in the long term [11].

Dorzolamide is one of topical carbonic anhydrase inhibitors that may be less systemically toxic. Topical dorzolamide has been found to have favorable anatomical and functional results in a number of studies of retinal disorders where there is fluid buildup. However, the literature on the direct comparison of the efficacy of oral and topical carbonic anhydrase inhibitors in CSC is limited.

Thus, the current study aims to assess and compare the efficacy and safety of oral acetazolamide and topical dorzolamide in patients with CSCs in terms of improvement in best-corrected visual acuity, central macular thickness, and resolution of subretinal fluid.

METHODOLOGY

This prospective, randomized, comparative clinical study was carried out in the Department of Ophthalmology of a tertiary care, teaching hospital for a period of 12 months after the approval from the Institutional Review Board and informed written consent was taken from all the subjects following the Declaration of Helsinki. Patients who presented with a clinical exam suggestive of central serous chorioretinopathy (CSC) were screened and enrolled based on this clinical exam and confirmation by spectral-domain optical coherence tomography (SD-OCT), which showed neurosensory retinal detachment (NRD) with subretinal fluid in the macula. Sample size was determined based on a minimum difference of 30 µm between the two mean values of central macular thickness reduction, a 95% confidence level, 80% power, a standard deviation of 50 µm and a possible attrition of 5 patients per group, giving a total of 100 patients. Patients were included if they were within the age range 18 to 60 years, had acute or chronic CSC, symptoms less than 6 months, subretinal fluid on OCT, and BCVA between 20/30 to 20/200; patients were excluded if they had any history of retinal laser therapy, photodynamic therapy, CNH, AMD, DR, uveitis, glaucoma requiring topical treatment, renal or hepatic dysfunction, electrolyte imbalance, sulfonamide allergy, pregnancy or lactation, or current systemic corticosteroid use. Participants who met the inclusion criteria were randomly allocated to either group without Group A were given oral acetazolamide 250 mg twice daily for 8 weeks, Group B were given dorzolamide hydrochloride 2% eye drops as topical drops (1 drop three times daily) for 8 weeks and treatment adherence was assessed at every follow-up visit. Baseline assessment comprised detailed history, best corrected visual acuity (BCVA) on Snellen charts converted to logMAR units, slit-lamp exam, Goldmann applanation tonometry, fundus exam, and SD-OCT assessment. OCT parameters measured were central macular thickness and maximum height of subretinal fluid, as well as documented complete resolution of the fluid. Visual acuity, OCT imaging, intraocular pressure and adverse effects were recorded at baseline, 4 weeks, 8 weeks and 12 weeks follow-up. The main outcomes were the change in central macular thickness compared to baseline at week 12 and the change in subretinal fluid height from baseline to week 12, and the secondary

outcomes were the change in visual acuity from baseline to week 12, complete resolution of subretinal fluid at week 12, and adverse effects of treatment. Data were analysed statistically using SPSS version 26, continuous data means ± SD, and categorical data presented as frequencies and percentages. Normality was evaluated by Shapiro–Wilk test and intergroup comparison was made with independent t-test, intragroup comparison was conducted using paired t-test, chi-square test was used for categorical variables and repeated measures ANOVA was used for analyzing longitudinal changes with p value < 0.05 considered statistically significant.

RESULTS

In total, 100 patients with central serous chorioretinopathy (CSC) were recruited and split into 2 groups of 50, one given oral acetazolamide and the other topical dorzolamide.

Table 1 shows that there were no statistically significant differences between the two study groups at baseline for any of the demographic or clinical variables. The mean ages were not different between the two groups (oral acetazolamide, 39.8 ± 8.5 years; topical dorzolamide, 40.4 ± 7.9 years; p = 0.71) with no age imbalance between groups. Males also showed a similar distribution in both the oral and topical groups with males being 76% of the former and 72% of the latter (p = 0.65), indicating equal sex representation between the two groups. The length of symptoms before treatment was also comparable (7.3 ± 2.1 weeks vs 7.6 ± 2.4 weeks, p = 0.54), and not likely to be a confounder of outcome. Groups were comparable for visual impairment at presentation as baseline functional status (BCVA, logMAR) was not significantly different (0.56 ± 0.15 vs 0.58 ± 0.14, p = 0.49). Similarly, anatomical severity (CMT) was virtually the same between the two groups (425 ± 64 µm vs 431 ± 61 µm, p = 0.62), showing that at the beginning of the study, the retinal disease burden was balanced between both groups.

Table 1. Baseline Characteristics

Variable	Oral Acetazolamide (n=50)	Topical Dorzolamide (n=50)	p-value
Age (years)	39.8 ± 8.5	40.4 ± 7.9	0.71
Male (%)	76%	72%	0.65
Symptom duration (weeks)	7.3 ± 2.1	7.6 ± 2.4	0.54
Baseline BCVA (logMAR)	0.56 ± 0.15	0.58 ± 0.14	0.49
Baseline CMT (µm)	425 ± 64	431 ± 61	0.62

Table 2 presents the results for visual acuity, which also found a statistically significant improvement for both treatment groups during the 12-week follow-up period. In the oral acetazolamide group, mean BCVA improved from 0.56 ± 0.15 at baseline to 0.25 ± 0.11 at week 12, with a mean improvement of 0.31 ± 0.10 logMAR (p < 0.001). Similarly, the topical dorzolamide group showed improvement from 0.58 ± 0.14 to 0.34 ± 0.12, with a mean gain of 0.24 ± 0.09 logMAR (p < 0.001). This suggests that systemic carbonic anhydrase inhibition had a greater impact on functional recovery in CSE patients.

Table 2. Comparison of Visual Acuity Outcomes (BCVA) Between Oral Acetazolamide and Topical Dorzolamide Groups at Baseline and Week 12

Group	Baseline BCVA	Week 12 BCVA	Mean Improvement	p-value
Oral Acetazolamide	0.56 ± 0.15	0.25 ± 0.11	0.31 ± 0.10	<0.001
Topical Dorzolamide	0.58 ± 0.14	0.34 ± 0.12	0.24 ± 0.09	<0.001

Table 3 shows that both treatment groups had statistically significant decreases in CMT during the 12-week follow-up period. The mean change in CMT in the oral acetazolamide group was from 425 ± 64 µm at baseline to 279 ± 41 µmat week 12, for a mean reduction of 146 ± 42 µm (p < 0.001). Similarly, the topical dorzolamide group showed a reduction from 431 ± 61 µm to 315 ± 48 µm, with a mean decrease of 116 ± 37 µm (p < 0.001).

The magnitude of anatomical improvement was similar between the two interventions; however, the oral acetazolamide group had a larger decrease in central macular thickness than the topical dorzolamide group.

Table 3. Changes in Central Macular Thickness (CMT) Following Treatment in Both Study Groups

Group	Baseline CMT (µm)	Week 12 CMT (µm)	Mean Reduction	p-value
Oral Acetazolamide	425 ± 64	279 ± 41	146 ± 42	<0.001
Topical Dorzolamide	431 ± 61	315 ± 48	116 ± 37	<0.001

Table 4 shows a clinically and statistically significant difference in the rate of complete subretinal fluid (SRF) resolution between the two treatment groups. Of the 39 patients who received acetazolamide orally, 39 (78%) had complete resolution of SRF by the end of follow-up while 11 (22%) had persistent fluid. The topical dorzolamide group had complete resolution in 30 patients (60%) and persistent SRF in 20 patients (40%).

Differences in anatomical recovery (complete SRF resolution) between the two groups were statistically significant (p = 0.048), with more successful outcomes achieved with the oral acetazolamide group.

Table 4. Comparison of Complete Subretinal Fluid (SRF) Resolution between Oral Acetazolamide and Topical Dorzolamide Groups

Outcome	Oral Acetazolamide	Topical Dorzolamide	p-value
Complete resolution	39 (78%)	30 (60%)	0.048
Persistent SRF	11 (22%)	20 (40%)	—

Table 5 shows the safety profile and occurrence of adverse effects in both treatment groups. Systemic adverse effects were reported more frequently with oral acetazolamide, including gastrointestinal upset (16% of patients) and paresthesia (20% of patients). In contrast, systemic side effects were not seen in the topical dorzolamide group.

In the other direction, the topical dorzolamide group (14%) had a higher rate of ocular irritation than the oral acetazolamide group (4%) due to the local tolerability concerns of topical therapy. Oral treatment also showed a slightly higher discontinuation rate (6% compared to 2%), which may have been because of systemic side effects that diminish compliance.

Table 5. Comparison of Safety Profile and Adverse Effects between Oral Acetazolamide and Topical Dorzolamide

Adverse Effect	Oral Acetazolamide	Topical Dorzolamide
Paresthesia	20%	0%
Gastrointestinal upset	16%	0%
Ocular irritation	4%	14%
Treatment discontinuation	6%	2%

DISCUSSION

Central serous chorioretinopathy (CSC) is an auto-regulating but potentially sight-threatening retinopathy which involves serous detachment of the neurosensory retina caused by choroidal hyperpermeability and dysfunction of the retinal pigment epithelium [12]. While many cases will recover on their own, if the disease is persistent or recurrent, or the initial attack is severe, therapeutic intervention is important in selected patients because it may prevent irreversible photoreceptor damage and long-term visual impairment. Both oral acetazolamide and topical dorzolamide significantly improved visual and anatomical outcomes in patients with CSC, and oral acetazolamide was more effective in improving VA, decreasing CMT, and achieving complete resolution of subretinal fluid [13].

There was a significant improvement in BCVA in both groups in our study but this improvement was greater in the oral group than in the topical dorzolamide group. This is similar to previous studies that indicated that systemic carbonic anhydrase inhibitors are more effective on the retinal pigment epithelium pump than topical agents, thus providing quicker resolution of neurosensory detachment [14]. In addition, García et al. found that oral acetazolamide improved fluid transport across the RPE and led to better functional results in patients with CSC, a result that is similar to our findings. In a

similar fashion, that acute CSC may benefit systemically with acetazolamide, but there are variable long-term outcomes [15].

Oral acetazolamide resulted in a significantly larger decrease in CMT than topical acetazolamide. The results of this study are consistent with the findings of Aljundi et al., who showed that carbonic anhydrase inhibition allowed them to resorb the fluid from the subretinal space, leading to measurable decreases in macular thickness seen on OCT imaging [16]. This increased effect of the oral therapy could be due to greater bioavailability of the drug in the systemic circulation and thus more uniform inhibition of carbonic anhydrase activity at the level of the RPE than topical therapy [17].

A higher percentage of the children in the oral acetazolamide group (78%) versus the dorzolamide topical group (60%) had complete SRF resolution. This difference is clinically important, and indicates that maybe systemic therapy could restore the anatomical status faster. Zha et al. also reported that oral carbonic anhydrase inhibitors led to quicker SRF resolution in acute CSC patients than conservative treatment [18]. Other studies Supuran et al. have pointed out, however, that CSC can often go away on its own and that the increases in benefit from pharmacologic treatment in mild cases may be relatively small, underscoring the importance of judicious selection of patients [19].

As far as safety is concerned, our study showed the systemic adverse effects of acetazolamide to be more common in the oral group, such as paresthesia and gastrointestinal discomfort, while the topical dorzolamide group was associated with mild ocular irritation. These results are in agreement with the known pharmacological activity of carbonic anhydrase inhibitors [20]. A systemic side effect of oral acetazolamide is carbonic anhydrase inhibition which can cause metabolic and neurological effects. Dorzolamide (topical) has low systemic absorption and has a more favorable safety profile [21].

The results of this study indicate that both oral acetazolamide and topical dorzolamide are effective in achieving clinical success in CSC, with oral acetazolamide having greater systemic side effects and associated benefits to the eye and other organs. Based on the severity, duration and tolerance of the disease, treatment selection should be individualized [22].

Although our findings have been positive, there are some limitations to our study. It was done in one center with a limited number of patients and a short period of follow-up. There were no measurements of long-term recurrence rate or long-term visual outcomes. Further multicenter randomized controlled trials with extended follow-up are suggested to further clarify the place of carbonic anhydrase inhibitors in the management of CSC.

CONCLUSION

Finally, both oral acetazolamide and dorzolamide topical treatment have been shown to be effective in achieving visual and anatomic outcomes in the treatment of central serous chorioretinopathy (CSCR), and both were associated with a dramatic decrease in central macular thickness (CMT), subretinal fluid (SRF), and improvement in visual acuity (VA). Oral acetazolamide has, however, been shown to be very effective in terms of greater visual improvement, higher percentage of complete resolution of subretinal fluid and more significant decrease in macular thickness, but has been shown to have a higher incidence of systemic adverse effects. By contrast, topical dorzolamide has a more favorable safety profile and a lower systemic side effect profile, presumably at the cost of its efficacy. Topical dorzolamide may thus be used in patients intolerant to systemic therapy or oral acetazolamide may be preferred when quick and more effective anatomical recovery is desired.

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