ROLE OF RIFAMPICIN AND KETOCONAZOLE IN CHRONIC CENTRAL SEROUS CHORIORETINOPATHY: A COMPARATIVE STUDY

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ABSTRACT

AIM

To compare the outcome of Rifampicin (RFN) & Ketoconazole (KTZ) in treatment of chronic central serous chorioretinopathy (CSCR).

TYPE OF STUDY

Prospective interventional case series.

MATERIAL & METHODS

It is a prospective study of 22 eyes of 22 patients having chronic CSCR who attended the ophthalmology OPD of a tertiary care hospital of Western Odisha from 1st March 2015 to 1st September 2015. All patients were male & belonged to age group of 25-60 years. Patients underwent examination using Snellen's chart, Direct & Indirect ophthalmoscope, Slit-lamp biomicroscopy with +90 D and Optical Coherence Tomography (OCT). Chronic cases were identified with OCT findings i.e. fibrinous aggregation at subretinal fluid & with history of unresolving CSCR of more than 6 weeks. 13 patients were given tab. RFN 600 mg per day orally for 4 weeks after evaluation in Pulmonary Medicine OPD to exclude Tuberculosis (TB). 9 patients were given KTZ 200 mg twice daily orally for 4 weeks. They were evaluated with OCT in their followup visits at 4 weeks after starting the treatment.

RESULTS

10 patients out of 13 having RFN and 5 out of 9 patients having KTZ showed decrease in fluid height in central macula and decreased aggregation of fibrinous exudates. After 4 weeks of RFN treatment, BCVA improved in 12 patients out of 13 (92.3%) and after KTZ treatment for the same period, BCVA improved in 5 patients out of 9 (55.6%). In RFN group, fluid height decreased from 250 µm±133 µm to 70 µm±123 µm (p=0.001) and in KTZ group fluid height decreased from 176 µm±110 µm to 78 µm±69 µm after 4 weeks of treatment (p=0.038).

CONCLUSION

RFN showed better result than KTZ in patients having chronic CSCR. But as Indian subcontinent is an endemic zone for TB and recent studies showing increasing prevalence of multi-drug resistant TB, we are suggesting KTZ for treatment of Chronic CSCR before opting for RFN. However, Liver function should be monitored when using KTZ.

KEYWORDS

Chronic Central Serous Retinopathy, Ketoconazole, Rifampicin, OCT in Chronic CSCR.

HOW TO CITE THIS ARTICLE: Choudhury D, Sharma P, Dora J. Role of rifampicin and ketoconazole in chronic central serous chorioretinopathy: A comparative study. J. Evid. Based Med. Healthc. 2016; 3(72), 3940-3944. DOI: 10.18410/jebmh/2016/841

INTRODUCTION: Central Serous Chorioretinopathy is an idiopathic retinal disorder characterised by localised serous detachment of the neurosensory retina at the macula.[1] It may occur secondary to leakage of fluid from choriocapillaries through one or more hyperpermeable RPE sites.[2] CSCR typically affects young adults in their middle age. Males are often more affected than females.[1] Various associated factors have been blamed; that include steroid administration in any form, Cushing's syndrome, Psychological stress, Helicobacter pylori infection, sleep apnoea syndrome, pregnancy, arterial hypertension, elevated catecholamine, genetic predisposition, Diabetes mellitus, Steroid producing tumors.[1]

Symptoms of CSCR are unilateral blurring of vision, metamorphopsia, micropsia and mild dyschromatopsia.[1] CSCR is divided into 2 categories i.e. acute and chronic type. Acute type most often resolves spontaneously. In chronic type, there is an extensive RPE changes resulting in chronic accumulation of SRF with frequent exacerbations and poor visual prognosis[1]. Many drug therapies have been trialled for treatment of chronic CSCR and many of the existing therapies are often ineffective. Thus, novel therapies to combat this frustrating disorder are always in need.[3] Treatment options like simple observation, discontinuation of the existing corticosteroid, micropulse diode laser

Financial or Other, Competing Interest: None.
Submission 04-07-2016, Peer Review 14-07-2016,
Acceptance 25-07-2016, Published 08-09-2016.
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DOI: 10.18410/jebmh/2016/841

application to the RPE leakage site, PDT, intravitreal Avastin has shown to be effective in certain extent.[1,4] Increased cortisol levels have been reported in CSCR patients.[5]

Drugs like Ketoconazole, Rifampicin that reduce synthesis of endogenous corticosteroid have been used to treat chronic cases of CSCR.[6,7] Ketoconazole is an imidazole derivative used for the treatment of various fungal infection that inhibits endogenous cortisol synthesis by inhibiting cytochrome P450 and 11-beta- hydroxylase enzyme. Hence, ketoconazole can be used in chronic CSCR cases which may act by reducing the endogenous cortisol level.[6] Rifampicin is an anti-TB drug. It inhibits DNA dependent RNA polymerase and blocks RNA transcription and is a cytochrome P450, 3A4 inducer, the enzyme which increases the metabolism of endogenous corticosteroid. Hence, Rifampicin is being used to treat chronic cases of CSCR.[7] Aim of our study is to compare the outcomes following treatment of Chronic CSCR with rifampicin and ketoconazole.

MATERIAL AND METHODS: A non-randomised prospective interventional study involving 62 eyes of 62 patients with acute CSCR (Less than two weeks) who have attended Ophthalmology OPD of a tertiary care hospital of Western Odisha from March 2015 to September 2015 was done after taking informed consent from patients and approval from Ethical Committee of the Institution. Initially, complete visual examinations including determination of spectacle best corrected visual acuity (SBCVA) using Snellen's chart, anterior and posterior segment examinations were performed on all patients using Direct Ophthalmoscope, Indirect Ophthalmoscope, Slit-lamp biomicroscopy with +90 D. Ocular Coherence Tomography (OCT) were performed to confirm the diagnosis. All the patients were treated with Tab. Acetazolamide 250 mg ½ tab twice daily orally, nepafenac eye drop 1 drop twice daily topically and ocular antioxidant tablet 1 tab once daily for 6 weeks. Then, the patients were evaluated after 6 weeks using OCT. 40 out of 62 patients showed complete resolution of subretinal fluid. But rest 22 patients showed persistence of Subretinal Fluid (SRF) and some showed fibrinous exudates in the SRF.

These patients were classified as Chronic CSCR and included in the study. Complete Blood Count, evaluation of hepatic enzymes, serum bilirubin, and serum creatinine were done before prescribing drug. 13 out of 22 patients were treated with 600 mg rifampin per day for 4 weeks and the rest 9 patients were treated with Ketoconazole 200 mg twice daily for 4 weeks. These patients were examined after 4 weeks of starting of treatment. The Best Corrected Visual Acuity (BCVA) was determined. Fundus biomicroscopy and OCT was performed to estimate the reduction of fluid height in central macular lesion. Fluid height is defined as the distance between RPE and IS-OS junction at central macular lesion.

Inclusion Criteria: Patients with CSCR who attended Ophthalmology OPD of a tertiary care hospital.

Exclusion Criteria: Patients with liver and kidney diseases, Patients with retinal diseases apart from CSCR.

RESULTS: 13 patients in the Rifampicin group and 9 patients in Ketoconazole group were studied. Mean patient age was 36±9 years (range 25-60 years) in the group who developed chronic CSCR. In Rifampicin group, mean age was 37±10.7 years (range 25-60) and in Ketoconazole group, mean age was 35±7 years (range 26-49). All patients were male in this study. According to table no. 1, at the time of presentation of these 22 patients, 6 patients had Visual Acuity of 20/80, 11 had 20/60 and 5 had 20/40.

VA	No. of Patients (n=22)	Percentage
20/40	5	22.7%
20/60	11	50%
20/80	6	27.3%

Table 1: Visual Acuity at Presentation in All Patients

According to table no. 2, after 6 weeks, just before starting of treatment 2 patients had Visual Acuity of 20/80, 5 patients had 20/60, 8 patients had 20/40 and 7 had 20/30.

VA	No. of Patients (n=22)	Percentage
20/30	7	31.8%
20/40	8	36.4%
20/60	5	22.7%
20/80	2	9.1%

Table 2: VA after 6 Weeks of Followup

According to table no. 3, at the end of 4 weeks after starting treatment, in Rifampicin group VA improved significantly coming back to 20/20 in 7 cases, 3 patients showed improvement of VA to 20/30 and 2 patients had 20/40. 1 patient did not show any visual improvement. He had VA of 20/80.

VA	No. of Patients (n=13)	Percentage
20/20	7	53.9%
20/30	3	23%
20/40	2	15.4%
20/80 (Non-improvement)	1	7.7%

Table 3: VA after 4 weeks of Treatment with Rifampicin

According to table no. 4, in Ketoconazole group after 4 weeks of starting treatment, VA improved significantly in only 2 cases to 20/20. 3 patients showed improvement of VA to 20/30 and 4 patients showed non-improvement of vision.

VA	No. of Patients (n=9)	Percentage
20/20	2	22.2%
20/30	3	33.3%
20/40 (Non-improvement)	1	11.2%
20/60 (Non-improvement)	3	33.3%

Table 4: VA After 4 weeks of Treatment with Ketoconazole

According to table no. 5, average fluid height at presentation was 288 µm±138 µm. After 6 weeks, just before starting treatment, average fluid height in all patients was 220 µm±127 µm. The differences in fluid height at presentation and after 6 weeks just before starting of treatment were not statistically significant (p=0.1). Mean fluid height after 4 weeks of treatment in all patients was 90±115 µm. The differences in fluid height in all patients before and after treatment were statistically significant (p=0.001).

At Presentation	At 6 weeks follow up	After 4 week t/t
288 µm±138 µm	220 µm±127 µm	90 µm±115 µm

Table 5: Fluid Height in All Patients at Presentation, At 6 Weeks of Followup and After 4 Weeks of Treatment

According to table no. 6, in Rifampicin group before starting treatment fluid height was 250 µm±133 µm and after treatment of 4 weeks it was 70 µm±123 µm. The differences at baseline in Rifampicin group were statistically significant (p=0.001). In ketoconazole group before starting treatment, fluid height was 176 µm±110 µm and after treatment of 4 weeks it was 78 µm±69 µm. The differences at baseline for Ketoconazole group were statistically significant (p=0.038). Figure no. 1, 2, 3 shows the gradual decrease in fluid height from the time of presentation to the end of treatment with Rifampicin.

	Before t/t	After t/t
Rifampicin Group	250 µm±133 µm	70 µm±123 µm
Ketoconazole Group	176 µm±110 µm	78 µm±69 µm

Table 6: Fluid Height Before and After Treatment for 4 Weeks with Rifampicin and Ketoconazole

According to table no. 7, 10 patients (77%) out of 13 having Rifampicin and 5 out of 9 patients (55.6%) having Ketoconazole showed significant decrease in fluid height in central macula and decreased aggregation of fibrinous exudates.

Group	Total No. of patient	No. of Patients Showing Decrease In Fluid Height	Percentage
Rifampicin	13	10	77%
Ketoconazole	9	5	55.6%

Table 7: No. of Patients Showing Decrease in Fluid Height after 4 Weeks of Treatment

During the review period, none of the patients in either group experienced deterioration in VA or progression of neurosensory detachment. No side effects of the drugs were noticed in all patients. Figure 1 shows the OCT finding of OS in CSCR, Figure 2 shows the fluid height decreased slightly at 6 weeks, figure 3 shows fluid height decreased significantly after 4 weeks of treatment with Rifampicin.

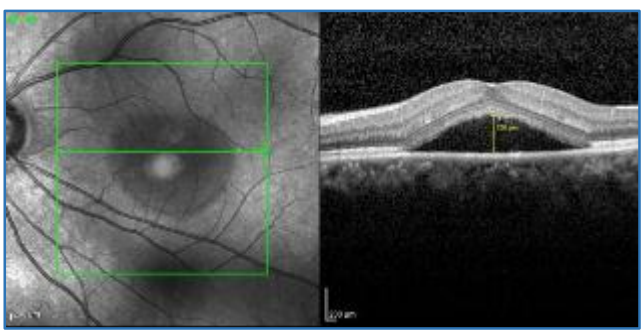

Fig. 1: OCT of OS showing CSCR

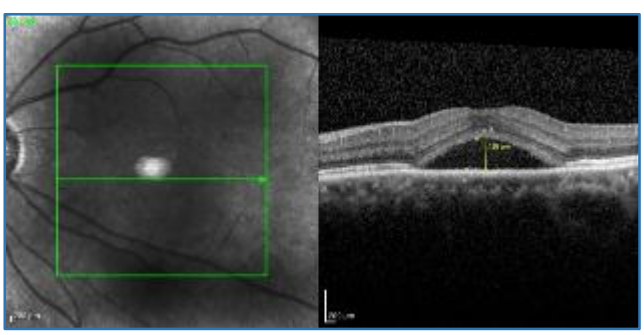

Fig. 2: Fluid Height Decreased slightly at 6 weeks of Followup

Fig. 3: Fluid Height Decreased Significantly After 4 Weeks of Treatment with Rifampicin

DISCUSSION: Exogenous glucocorticoid delivered via any root like oral, intravenous, intramuscular, inhaled, intranasal, intra-articular, epidural, periocular or epidermal application may induce CSCR.[8-10] In many instances, elevated endogenous glucocorticoid production has been found in CSCR cases. Carvalho-Recchia et al (2002) investigated 50 patients with acute symptoms and clinical manifestation of CSCR and found 52% of them to have a history of exogenous steroid use.[11] Haimovici et al (2003) tested patients with acute CSCR for elevated 24-hour urine cortisol or tetrahydroaldosterone levels and found increased levels in 50% of cases.[12] Corticosteroids have also been shown to induce increased capillary fragility and hyperpermeability, leading to leakage of fluid in the subretinal space.[13] Bouzas et al. (2002) reported cortisol may generate alterations in the transport of ions and H_2O instigated by mineralocorticoid receptors on the RPE.[14] Smith (1984) postulated that direct damage by glucocorticoids on RPE cells and their tight junctions may be the causative factor of CSCR.[15] Both findings would support a potential localized impairment of RPE functions as a cause for CSCR. Massive amount of SRF may be present in some cases (Figure no. 4).

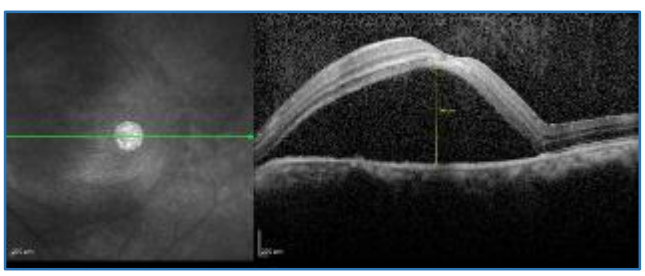

Fig. 4: Massive Fluid Height in a Patient with CSCR

Ketoconazole is an imidazole derivative used for treatment of various fungal infections. It binds to fungal cytochrome P450 enzymes and destroys the cytoplasmic membrane. It inhibits endogenous cortisol synthesis by inhibiting cytochrome P450 & 11-β- hydroxylase enzyme so that the precursor molecule of cortisol i.e. pregnenolone can't be formed from 11-β- deoxycortisol. Hence Ketoconazole can be used in chronic CSCR cases which may act by reducing the endogenous cortisol level.[6] Because of its anti-cortisol effect, Jampol et al. (2002) has already proposed ketoconazole as a candidate therapy in the treatment of CSCR.[15] Meyerle et al. (2007) treated 5 patients with chronic CSCR with ketoconazole 600 mg/ day for 4 weeks. Monitoring over 24 hours showed a decrease in urinary cortisol levels.[16]

Rifampicin is an anti- TB drug. It blocks RNA transcription by inhibiting DNA- dependant RNA polymerase. It's a cytochrome P450, 3A4 inducer, the enzyme which increases the metabolism of endogenous corticosteroid. It leads to improvement of clinical pictures of CSCR.[3] Ravage et al studied the therapeutic effects of Rifampicin on four patients. Active time of CSCR in these patients ranged from less than a month to more than a year. All patients were found to be male with a mean age of 50 years. The patients were treated for 4 weeks.

The average thickness change of Central Macular Thickness was-99 (167±SD) in the first week, and -102 (215±SD) in the eighth week-93 (91±SD) in the twelfth week and the visual gain has been from zero to ≥3 lines.[17] However, Rifampicin-resistant M. Tuberculosis isolates from patients with TB who received Rifampicin monotherapy were reported.[18] Our study evaluated ketoconazole in 9 cases and Rifampicin in 13 cases in the treatment of chronic CSCR and compared the results of both groups. By contrast with the outcome in patients with chronic CSCR described by Meyerle et al (2007),[16] we found an improvement in VA and a decrease in neurosensory or RPE detachment in patients with chronic CSCR after 4 weeks of treatment with Ketoconazole ($p = 0.038$). Patients treated with Rifampicin showed better improvement of vision and more decrease in fluid level than Ketoconazole ($p=0.001$). Limitation of our study is the small sample size taken. More number of patients should be added to get a definitive result.

CONCLUSION: Rifampicin showed better result than Ketoconazole in patients having chronic CSCR. But as Indian subcontinent is an endemic zone for TB and recent studies showing increasing prevalence of multidrug resistant TB, we are suggesting Ketoconazole for treatment of Chronic CSCR before opting for Rifampicin. However, an option for initial therapy with Rifampicin in chronic bilateral CSCR cases where one eye with poor vision from previous CSCR and one eyed individual with chronic CSCR may be taken into consideration. Hence, in our view it is better to use Ketoconazole in chronic CSCR cases. However, LFT should be monitored when using Ketoconazole.

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