Original Article

Sulfadiazine Plus Clindamycin and Trimethoprim / Sulfamethoxazole Plus Clindamycin Versus Standard Treatment for Therapy of Ocular Toxoplasmosis

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Purpose: To compare efficacy and side effects of clindamycin plus sulfadiazine and Trimethoprim / sulfamethoxazole plus clindamycin, with pyrimethamine plus sulfadiazine for treatment of toxoplasma chorioretinitis.

Material and Methods: Descriptive case series study.

Results: Of 79 toxoplasma retinochoroiditis patients, 41, 16 and 22 patients were treated with standard treatment, clindamycin plus sulfadiazine (group1) and Trimethoprim / sulfamethoxazole plus clindamycin (group2) respectively.

Visual acuity of three groups improved similarly, with no significant difference between them (6/21 ± 6/32, 6/24 ± 6/70 and 6/21 ± 6/37 in standard group, groups 1and 2 respectively) (PV: 0.496). Decrease in activity of lesions began 27.2 ± 7.62, 27.8 ± 12.6 and 28.6 ± 8 days after treatment in standard group, group 1 and 2 respectively (PV: 0.572). Vitreal inflammation also began to decrease similarly in three groups (PV: 0.152).

The frequency of adverse drug effects leading to treatment interruption was highest in group 2 (14%) with mild side effects observed in 31.7% of them.

Conclusion: The efficacy of 3 regimens was similar, but highest frequency of side effects was associated with trimethoprim / sulfamethoxazole plus clindamycin, if careful monitoring of adverse drug effects is impractical it is not recommended.

Currently standard treatment for treatment of ocular toxoplasmosis consists of pyrimethamine and sulfadiazine supplementd by folinic acid. It is not readily available in some areas[1]. There are other possible therapies for toxoplasmosis. Clindamycin acts synergistically with pyrimethamine and sulfonamides[2] with good ocular penetration in the choroid[3]. Trimethoprim / sulfamethoxazole has been used in the treatment of toxoplasmosis. Although it is less active than the combination of pyrimethamine and sulfadiazine, but does not have hematologic toxicity as frequently as standard treatment, is inexpensive, is readily available and has been used alone or in combination with clindamycin[1, 4]. The purpose of our was to evaluate practical options for clinicians practicing in areas with limited choices and inconsistent supply of sulfadiazine, pyrimethamine and folinic acid, we reviewed medical records of 141 patients with clinically diagnosed toxoplasmic retinochoroiditis to compare efficacy and side effects of standard treatment, combination of clindamycin with sulfadiazine and clindamycin plus trimethoprim/sulfamethoxazole.

MATERIAL AND METHODS

Medical records of patients referred by ophthalmologists with clinical diagnosis of toxoplasmic

retinchoroiditis to an infectious disease clinic in Yazd from July 2001 To June 2010 were reviewed. The need for an anti-parasitic drug was determined by an ophthalmologist and treatment was carried out by infectious disease specialist. Indications for therapy were as follow: severe vitritis, posterior pole lesions, papilitis, large lesions and when lesions were near arcades and optic disk. Exclusion criteria were: charts of patients with diabetes mellitus as comorbidity, pregnancy (because oral prednisolone was not given to them), visual acuity in Snellen metric scale (VA) less than 6/30 at initial evaluation so that visual acuity could be taken as a continuous variable for comparison. Another reason for excluding patients with VA<6/30 was that most of them had been treated by standard regimen because of ethical concern. Data was collected by completing a checklist for each patient's medical record. Charts including information about visual acuity, trend of severity of vitreous inflammation ,VA at the end of treatment, size of lesions in terms of optic disk diameter (DD), their location (by drawing), presence of vasculitis, optic disk edema, macular edema and report of anti-toxoplasma IgG & IgM were entered into study. Main outcome measures were decrease in severity of vitreous inflammation (graded as trace to ++++), interval between initiation of therapy and time of beginning of decrease in activity of chorioretinitis. Response to treatment was defined as: flattening of lesion, reduction in vitreous inflammatory reaction, (at least1+ reduction), disappearance of edema of disk, macula and retina, sharpening of lesion borders, beginning of pigmentation and scar formation.

Standard treatment consisted of an initial dose of 100mg Pyrimethamine, followed by 50mg daily, sulfadiazine 1000 mg Q 6h with supplement of 5mg calcium folinate per day.

Patients treated with clindamycin (300 mg Q6h), sulfadiazine (1000 mg Q6h) were designated as group 1 and those who have been treated with clindamycin (300 mg Q6h) plus trimethoprim/ sulfamethoxazole (960 mg every 12 hours) were designated as group 2.

Oral prednisolone was given similarly to all of them, 1.2 mg/kg per day at third and fourth days (for two days), then 0.8 mg/kg daily for 17 days before tapering.

Adverse drug reactions had been monitored in all patients in each visit, but CBC and platelet count had been done once in each patient receiving standard treatment at about the third week.

Mean of visual acuity before and after treatment, duration mean (in days) to achieve best visual acuity, mean of interval between initiation of treatment and beginning of decrease in activity of retinal lesions, and mean of duration of therapy were compared by Kruskal Wallis test, the chi square test was employed to compare: levels of visual acuity before and after treatment, period between initiation of therapy and beginning of reduction in vitreous inflammation in each group, distribution of gender and age, percentage of recurrent lesions, location of lesions in relation to fovea, severity of vitreous inflammation, size of lesions before treatment. Analysis was performed by SPSS11.5 version and p value of 0.05was taken as significant.

Frequencies of side effects were calculated by dividing the events observed by the number of patients exposed to each treatment group (i.e. 43, 21 and 35 in standard treatment group, group1and 2 respectively).

RESULTS

Medical records of patients who were treated as toxoplasma chorioretinitis in infectious disease clinic in Yazd from July 2001 To June 2010 were reviewed. One hundred and forty one patients' medical records were eligible for study. Medical records of 34 patient were excluded due to visual acuity < 6/30 in either eye (because all of them had been treated with standard regimen due to ethical concern, so their visual acuity could not be compared between groups as a continuous variable), diabetes mellitus and pregnancy (because they had not received prednisolone and their rate of vitreous reaction resolution could not be compared between groups). Of 107 patients, 51 patients had received standard treatment, 21 patients, sulfadiazine plus clindamycin and 35 patients, trimethoprim / sulfamethoxazole plus clindamycin.

Ten patients in standard treatment group were excluded from analysis due to lost to follow up (n=7), discontinuation of drugs because of skin allergy (n=2) and vomiting (n=1). Five patients in group 1 were excluded from analysis due to lost to follow up because of depression (n=1), discontinuation of treatment because of skin allergy (n=1), diarrhea (n=1), epigastric pain (n=1) and inadequate initial evaluation (n=1). Thirteen patients in group 2 were excluded from analysis due to: lost to follow up (n=6), inadequate initial evaluation (n=2), discontinuation of treatment due to diarrhea (n=3) and gastrointestinal upset (n=2).

Seventy nine patients (35 males, 44 females) including 41 patients in standard treatment group, 16 patients in sulfadiazine plus clindamycin group and 22 patients in trimethoprim / sulfamethoxazole plus clindamycin group had completed at least 28 days of the course of therapy who were compared regarding efficacy and adverse effects.

There was no statistically significant difference between 3 groups with regard to age, gender, initial visual acuity and after visual acuity after treatment, improvement in visual acuity, interval between initiation of therapy and beginning of decrease in activity of lesions, mean time to achieve best visual acuity, location of lesions in relation to fovea, initial severity of vitreous inflammation, size of lesions (Table1).

The treatment groups responded similarly to treatment with improved VA. Range of patient's initial visual acuity was 6/30 – 6/6 in the standard therapy group, 6/21-6/6 in the sulfadiazine plus clindamycin group and 6/30-6/6 in the TMP/SMX plus clindamycin group (P=0.803). Range of patient's visual acuity achieved after treatment was 6/9-6/6 in the standard group, 6/9-6/6 in group1 and 6/12-6/6 in group 2.

Within each group there was seen significant improvement in VA after treatment: VA increased by 6/21 in standard group (P=0.000), by 6/24 in group1 (P=0.002) and by 6/21 in group2 (P = 0.001). However there was no statistically significant difference in visual improvement between the 3 treatment groups (P=496).

Excluding those patients who had full VA (6/6) before treatment, visual acuity improved in all cases after treatment, except for 2 patients in group 2, who's initial VA had not been determined. None of patients had post- treatment VA less than 6/12 (table 2). Effect of therapy on the beginning of reduction of vitreous inflammation is presented in table 3.

In standard treatment group, frequency of adverse effects leading to discontinuation of treatment was 7.8% (4 out of 51 exposed patients), 3 due to skin hypersensitivity and 1 due to nausea, vomiting and burning sensation in the skin. Other less severe adverse effects were 3.9% renal colic (2 patient), 7.8% nausea and vomiting (4 patients), 5.9% gastrointestinal upset (3 patients), 2 cases of diarrhea and 1 case of abdominal pain. Total frequency of adverse effects was 31.3%.

In group 1 frequency of adverse effects leading to discontinuation of treatment was 14.3% (3 of 21 patients), 1 due to diarrhea, 1 due to cutaneous hypersensitivity and 1 due to drowsiness).

In group 2, 14.3% of patients (5 of 35 patients), 3 with diarrhea, 2 with gastrointestinal upset discontinued their treatment, frequency of other less sever adverse effects observed were 17.3% mild diarrhea (6 patients), 8.6% mild gastrointestinal upset (3 patients) and 5.7% cutaneous hypersensitivity (2 patients) totally constituting 46% of those initially exposed. Suboptimal dose consumption of drugs was observed only in this group, which may has been due to drug intolerance, although not mentioned by patients specifically. All of the adverse effects were reversible in 3 regimens.

DISCUSSION

Our study revealed no significant difference between standard treatment, sulfadiazine plus clindamycin and TMP/SMX plus clindamycin for toxoplasma retinochoroiditis in terms of improvement in visual acuity. In other similar studies there has been observed no difference in improvement of visual acuity, which is consistent with our findings[1, 5]. However mean of improvement in VA have been higher than our study (6/18 to 6/21 versus 6/24-6/21 in the present study) which can be explained by two factors i.e. we excluded all patients with VA less than 6/30 from the study greater proportion of our patients had initial VA 6/6 compared with other studies for example that by Soheilian[1].

Regarding mean time to achieve best visual acuity, which was 32, 32.7 and 33.3 days in the regimens mentioned above respectively, again no significant difference was observed. In the study done by Soheilian et al this period was 35.4 days for standard treatment group and 32.8 days for TMP/SMX treatment group[1].

The frequency of skin rash observed with standard therapy in this study (7 %) was slightly higher than the study done by Bosch-Driessen et al (5%), [6] and much higher (due to higher dose of sulfadiazine in the present study) than Soheilian et al's study (2.8%),[1] but obviously lower than a study by Theaudin et al (2 out of 7 patients), whose patients had higher mean of age with more extensive disease.[7] Some of other side effects observed in this study were mentioned by Bosch – Drissen LH et al's study[6].

Table 1: Characteristics of patients with toxoplama chorioretinitis before and after treatment (N = 79%)

	Sulfadiazine + Clindamycin N = 16 n (%)	Standard Treatment N = 41 n (%)	Co-trimoxazole + Clindamycin N = 22 n (%)	P-value
Male	9 (56.2)	16 (39)	20 (45.5)	0.657
Female	7 (43.7)	25 (61)	12 (54.6)	
Age, y (range)	23.2 ± 7 (13 - 42)	23.47 ± 8.46 (13 - 48)	23.3 ± 7.8 (11 - 47)	0.847
Mean of initial VA †	6/7.5 ± 6/30	6/75 ± 6/24	6/9 ± 6/30	0.463
Mean of VA after Treatment	6/7 ± 6/60	6/7 ± 6/70	6/7 ± 6/48	0.117
Improve in VA	6/24 ± 6/70	6/21 ± 6/32	6/21 ± 6/37	0.868
Time to achieve best VA (days)	32.7 ± 12.6	33.7 ± 11.6	33.3 ± 10	0.85
Interval between treatment and start of decrease in activity of lesions (days)	27.8 ± 12.6	27.2 ± 7.62	28.6 ± 8.4	0.572
Duration of treatment (days)	43.64 ± 8.65	41.4 ± 8.25	41 ± 4.95	0.789
Recurrent lesions (%)	11/16 (68.7)	26/41 (64)	19/22 (86.4)	0.17
Lesions near fovea	11/15 (73.3)	24/41 (59)	11/20 (55)	0.37
Vitreous cells before therapy				
Trace - 2%	6/14 (42.8)	24/41 (58.8)	15/22 (68.2)	0.2
3+ - 4+	8/14 (57.2)	17/41 (41.2)	7/22 (31.8)	

VA: Visual acuity in Snellen lines

Table 2: Visual acuity (Snellen lines) before and after treatment

	Before N = 77 n (%)			After N = 79 n (%)		
	Sulfadiazine + Clindamycin Group	Standard Treatment Group	TMP / SMX + Clindamycin Group	Sulfadiazine + Clindamycin Group	Standard Treatment Group	TMP / SMX + Clindamycin Group
6/12 - 6/6 (%)	12 (85.7)	34 (82.9)	19 (86.4)	16 (100)	41 (100)	22 (100)
6/30 - 6/15 (%)	2 (14.3)	7 (17.1)	3 (13.6)	0 (0)	0 (0)	0 (0)
Total	14 (100)	41 (100)	22 (100)	16 (100)	41 (100)	22 (100)

P-value: 0.681

Table 3: Effect of therapy on the beginning of reduction* of vitreous inflammation N = 79

	No of Patients n (%)			
Beginning in Reduction of Vitreal Inflammation	Sulfadiazine + Clindamycin N = 16	Standard Treatment N = 41	TMP - SMX + Clindamycin N = 22	Total N = 79
Less than 3 weeks	9 (56.3)	15 (36.6)	6 (31.6)	29 (40.8)
3 to 6 weeks	4 (25)	21 (51.2)	11 (42.1)	32 (45.1)
More than 6 weeks	3 (18.7)	4 (12.2)	5 (26.3)	10 (14.1)

P-value: 0.681

Total adverse drug side effects in the present study (18.1%) with standard therapy (except for bone marrow side effects of pyrimethamine which may be under reported due to monitoring CBC infrequently) are of much less than the frequency (64%) than observed by Bosch-Drissen LH et al in their study[6].

The frequency of serious adverse effects in clindamycin plus sulfadiazine group is less than the study by Rothova A et al (17% versus 14.3% in this study) with similar dosage used in two studies although we treated patients longer than them (4 weeks versus 6 weeks in the present study)[4]. But the frequencies of adverse effects in TMP/SMX plus clindamycin were higher than both studies (2.8% in Soheilian M et al's study and 4% in Rothova A et al's study). This is probably due to addition of clindamycin, higher dose and longer duration of treatment than Rothova A et al's study[4].

The reason we choose 6 weeks as the preferred duration of treatment was our previous observation that more relapse had occurred in patients whose duration of therapy was shorter (μ=38 days) than those with 42 days duration. (published in Bina Journal of ophthalmology, scientific journal of Eye bank of IRI, Vol. 7, No. 3, Spring 2002).

In the present study none of 3 regimens was statistically different from others regarding influence on vision, inflammatory activity and beginning of decrease in activity of lesion. In a physician survey among uveitis specialists in USA no consensus regarding the choice of anti parasitic agents for treatment regimens was present as well[8]. So it can be concluded that: the frequency of adverse side effects especially those leading to discontinuation of drugs determines the preferable regimen. The least preferable regimen in this study was TMP / SMX plus clindamycin with total 46% adverse effects and the standard regimen was best tolerated by our patients.

Limitation in the present study was that CBC platelet has been done only once during the treatment, which may have led to underestimation of bone marrow suppression because of pyrimethamine.

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