CHRONIC TRACHOMA: COMPARISON OF AZITHROMYCIN VERSUS TOPICAL TETRACYCLINE IN RURAL SINDH POPULATION

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ABSTRACT

Objective: To compare the efficacy of oral azithromycin with topical tetracycline for treating chronic trachoma in rural Sindh population of Pakistan.

Study Design: Randomized Control Trial (RCT).

Place and Duration of Study: CMH Pano Aqil from October 2010 to September 2013.

Material and Methods: A total of 214 individuals with active trachoma in at least one eye were recruited in the study and randomly assigned to either treatment group. Patients visited after 10 weeks. The outcome was 'resolved disease'.The data was analyzed using SPSS 20.

Results: Patients in azithromycin group were significantly more likely to have resolved disease as compared to tetracycline group at 10 weeks of follow up(86% vs 71%; 95% confidence interval CI, 0.28-0.87; *p*=0.015). Differences within the age groups were not significant (children, *p*=0.072; elderly, *p*=0.091).

Conclusion: Single dose oral azithromycin was significantly more likely to achieve better outcome in chronic trachoma in rural population where compliance had been an issue.

Keywords: Trachoma, Antibiotic, Azithromycin, Tetracycline, Drug therapy.

INTRODUCTION

Trachoma is chronic keratoconjunctivitis caused by obligate intracellular bacterium Chlamydia trachomatis[1]. It is the leading cause of preventable blindness[2]. It is estimated to be endemic in 53 countries and 229 million people are at risk of infection. It is responsible for visual impairment in 2.2 million people, of whom 1.2 million are irreversibly blind. Women are blinded 2-3 times more often than men[3]. Prevalence of conjunctivitis in desert areas of Sindh is estimated to be 12.87%[4]. Disease transmission occurs primarily between children and their mother[5]. Repeated episodes of infection and re-infection cause chronic follicular conjunctivitis (TF)or intense conjunctival inflammation (TI) which lead to tarsal conjunctival scarring (TS). The scarring distorts the upper tarsal plate and leads to entropion and trichiasis (TT) which by causing physical injury to cornea ultimately leads to corneal opacity (CO)[6]. Chlamydial serotypes causing this blinding trachoma are A, B, Ba and C. Whereas serotypes D-K causing genital infection in young age often cause subacute follicular conjunctivitis resembling chronic trachoma but is free of blinding complications. Active trachoma is most commonly seen in pre/primary school children presenting with follicular trachoma with intense conjunctival inflammation and middle aged individuals (their grandparents) presenting with trichiasis and corneal opacity. However these signs are not age specific, therefore follicles, scarring and trichiasis may all be seen in same patient.

International efforts to control the disease are based on SAFE strategy which combines Surgery, Antibiotics, Facial cleanliness[7] and Environmental improvement for the Global Elimination of Trachoma by the year 2020 (GET2020)[8]. Two antibiotic regimens are currently recommended for active disease;1.tetracycline eye ointment (OxytetracyclineHCl 1% w/w) applied twice daily for six weeks (2) single dose oral Azithromycin (20 mg/kg BW)[9]. Azithromycin is derivative of erythromycin with an extra methyl substituted N at position 9 in lactone

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ring, which enhances its bioavailability, leading to sustained tissue concentration and concentration at site of inflammation[10].

MATERIAL AND METHODS

A parallel group randomized controlled trial was conducted to compare the efficacy of single dose oral azithromycin with topical tetracycline at Combined Military Hospital, Pano Aqil Cantonment from October 2010 to September 2013. Consent was received from hospital ethics committee. Availability of the medicines at the medical stores was ensured. Azithromycin was received as a donation. Children aged 5-9 years and elderly individuals above 55 years reporting in CMH Pano Aqil with chronic irritation, watering or redness and showing any signs of chronic trachoma like follicles, scarring, trichiasis or corneal opacity were included in the study. Exclusion criteria included patients having history of allergic reaction to either of the drug.

After explaining the procedure, consent from the patients and attendants was sought. Study group was assigned on the basis of simple randomization. Group allocation was concealed from the participants before they had been recruited into the study. Patients received the drug based on the number enrolled in the register, the first patient received tetracycline, the second azithromycin and so on. Children were weighed and single dose of syrup azithromycin was given by nursing staff. Elderly patients were given 3 tablets each of 500mg azithromycin with sip of water in outpatient department. First dose of topical tetracycline was administered to both eyes by nursing staff in front of attendant. The rest of the tube and a complete second tube of ointment were handed over to the attendant with instructions to apply the ointment in the same way, twice daily for six weeks. For follow-up all patients visited 10 weeks after treatment was started. Both eyes were examined and graded by ophthalmologist who was blinded to treatment allocation. Disease was said to be cured if the clinical signs of active disease had resolved in both eyes at follow-up. The data was entered and analyzed using SPSS 20.

A total of 214 individuals (135 children less than 9 years of age and 79 elderly above 55 years of age) with active trachoma (TF or TI) in at least one eye were recruited into the study. Nineteen (8.8%) of these patients had intense inflammation (TI). There was no significant difference in age/sex in frequency of TI. At 10 weeks follow up, 204(95%) patients were traced. 10 patients were lost to follow up (Table-1). Thus 204 patients were catered for results. One hundred ans six patients out of 204 (52%) had received oral azithromycin and 98 patients out of 204(48%) had received topical tetracycline.

RESULTS

At 10 weeks, subjects who were disease free were counted as 'resolved disease' (positive outcome). Overall 161 out of 204(79%) were of positive outcome who had received either of the treatment. In azithromycin group, 91 out of 106(86%) had resolved disease and 15 out of 106(14%) were showing some form of disease. In tetracycline group, 70 out of 98(71%) had resolved disease and 28 out of 98(29%) were showing some form of the disease. Subjects receiving azithromycin were significantly more likely to have resolved disease than those allocated to tetracycline, at 10 weeks (p=0.015). Azithromycin appeared to be more effective than tetracycline in curing intense inflammation (TI); 8 out of 10 subjects (80%) were cured after receiving azithromycin while in tetracycline group, 2 out of 9(22%) were observed to have cleared disease.

Out of 204 total patients, 129 were children (63%) less than 9 years of age. And 75 were elderly (37%) above 55 years of age. One hundred and eight children out of 129(84%) showed positive outcome and 21 children out of 129 (16%) showed some form of the residual disease. In azithromycin group, 60 children out of 67(90%) had resolved disease while 48 out of 62 (77%) had resolved disease in tetracycline group. Fifty three out of 75 elderly patients (70%) had resolved disease while 22 out of 75 elderly patients(30%) were still showing some form of the residual disease. Thirty one elderly out of 39 (79%) had resolved disease in azithromycin group while 22 elderly out of

36(61%) had resolved disease in tetracycline group. (Table-1,2).

DISCUSSION

Trachoma is caused by recurrent, chronic infection of the eye with Chlamydia trachomatis and progresses from inflammation to conjunctival scarring, lid deformity, corneal abrasion and visual impairment. It is the most common infectious cause of blindness[11]. It is common in low socioeconomic groups and associated with poor sanitation[3]. Active trachoma is routinely treated with tetracycline eye ointment applied twice daily for six weeks. However poor compliance is observed as it is difficult and uncomfortable to apply, causes visual blurring and has long duration of treatment. Systemic antibiotics tested in randomized controlled trials have shown efficacy against active trachoma and a single dose of azithromycin has been shown to reduce recurrence rates following trichiasis surgery[12,13] as well. This clinical trial (antibiotic arm of SAFE strategy) was designed to compare single dose oral azithromycin with topical tetracycline eye ointment applied twice daily for 6 weeks. This individually randomized controlled trial show that oral azithromycin is more effective(86% resolved disease) than topical tetracycline for clinical cure of chronic trachoma(71% resolved disease) in either of age group, children or elderly at 10 weeks of follow up. In terms of disease resolution, tetracycline appeared to perform as well, if not better than azithromycin during this period of follow up, but it might be explained by the long (6 weeks) period of tetracycline treatment.Because trachoma is a chronic disease and reinfection is common, treatment must be evaluated at 1 year follow up to allow for the autumn epidemic of purulent conjunctivitis, a source for disease spread. This was not possible as most of our patients are not traceable by that time.

Bailey et al[14] in their study 'Randomized controlled trial of single dose azithromycin in treatment of trachoma' concluded that 78%

Table-1: Baseline characteristics of participants in intervention.

Characteristics	Azithromycin group n= 106 (%)	Tetracycline group n=98 (%)	*p*-value
Age			**>0.99**
5-9 years	67 (63.2%)	62 (63.3%)	
>55 years	39 (36.8%)	36 (36.7%)	
Female sex	60 (56.6%)	51 (52.0%)	0.57
Patients with TI	10 (0.094%)	9 (0.092%)	>0.99

Table-2: Result and analysis.

Drugs	Negative outcome n (%)	Positive Outcome n (%)	Total n	Relative Risk (RR)	95% Confidence Interval (CI)	*p*-value
Overall						
Azithromycin	15 (14.15%)	91 (85.85%)	106			
Tetracycline	28 (28.57%)	70 (71.43%)	98			
Total	43 (21.07%)	161 (78.93%)	204	0.4953	0.28-0.87	0.015*
Children						
Azithromycin	7 (10.45%)	60 (89.55%)	67			
Tetracycline	14 (22.58%)	48 (77.42%)	62			
Total	21 (16.28%)	108 (83.72%)	129	0.4627	0.20-1.07	0.072
Elderly						
Azithromycin	8 (20.51%)	31 (79.49%)	39			
Tetracycline	14 (38.89%)	22 (61.11%)	36			
Total	22 (29.33%)	53 (70.67%)	75	0.5275	0.25-1.11	0.091
Patients with TI						
Azithromycin	2 (20%)	8 (80%)	10			
Tetracycline	7 (77.78%)	2 (22.22%)	9			
Total	9 (47.37%)	10 (52.63%)	19	0.2571	0.07-0.93	0.039*

*Statistically significant.

were having resolved disease in azithromycin group as compared to 72% in tetracycline group. Tabbara Fet al[15] in their randomized control study found 63.3% patients of resolved trachoma who received azithromycin compared with 65.4% who were treated with tetracycline ointment. They found no significant difference in treatment effect or baseline characteristics between treatment groups. Both treatments were well tolerated, and no adverse events were noted.

The probable factors leading to the significant difference in outcome could be not applying the topical ointment regularly as taught, patient motivation to continue with therapy once some benefit had been achieved and hygiene practices. Even though our study showed an overall significant difference between the two groups, when stratified by age, the differences were not significant. Although azithromycin is relatively expensive as compared to tetracycline eye ointment, we are administering it only to patients with active disease. Considering the repeated doses of eye ointment which is uncomfortable and blurs vision, compliance to treatment schedule is probably affected.Our patients belonged to suburbs of PanoAqil (Rural Sindh) living in overcrowded compounds in near proximity to livestock. As level of education was also very poor, therefore non treatment, under treatment or long treatment will cause high chances of spreading the disease. Despite comprehensive patient education, only 71% disease resolution was achieved in tetracycline group as compared to 86% in azithromycin group.In settings with undertrained staff and overburdened facilities, the rates may even be lower for tetracycline group as patient education may be compromised, affecting compliance. Although cost of treatment with azithromycin will be higher but better compliance, good results and high morbidity associated with untreated trachoma nullifies this argument. Although azithromycin costs more, but better compliance and proportion of cured patients is probably worth the greater price. Significant morbidity associated with untreated trachoma especially merits the use of a drug that leads to better compliance and hence cure.

In cases of TI, use of azithromycin as first-line therapy appears to have significant merits since discomfort in TI due to associated vascular dilatation and tissue edema is further provoked by topical treatment[16].

Our study was limited by the relatively small sample size. The results need to be backed up by further similar trials in other rural areas of the country. If substantial evidence is collected, azithromycin should be the first-line treatment- especially in areas where trachoma is not endemic and mass treatment of population is not required. This can lead to better resource allocation because saving on the costs of drugs results in greater recurrence and complications which puts a burden on the healthcare resources that we were saving in the first place. Secondly, our study did not address the reasons for the different rates of disease resolution. Future studies can study issues such as compliance, hygiene practices and living conditions and their impact on the outcomes of antibiotic therapy in trachoma.

CONCLUSION

Single dose oral azithromycin and topical tetracycline both have high cure rate in active trachoma. Azithromycin was significantly more likey to lead to better outcomes in trachoma in our setting. Differences within age groups were not significant. Azithromycin should become the first-line treatment of trachoma in non-endemic rural areas of the country.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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