Objective: To determine whether treatment with oral azithromycin compared with topical tetracycline reduces the recurrence of trichiasis for up to 3 years following surgery for trichiasis.

Methods: The Surgery for Trichiasis, Antibiotics to Prevent Recurrence (STAR) trial is a randomized, single-masked, clinical trial conducted in southern Ethiopia, a region where trachoma is hyperendemic. A total of 1452 patients who underwent trichiasis surgery were randomly assigned at a 2:1 ratio to either a single dose of oral azithromycin (1 g) or topical tetracycline (twice per day for 6 weeks) following surgery.

Main Outcome Measures: Recurrence of trichiasis within 3 years following surgery.

Results: The rate of recurrence was 10% in the azithromycin group and 13% in the tetracycline group. The azithromycin group had a 22% reduction in recurrence of trichiasis 3 years after surgery compared with the tetracycline group (P = .13). Severity of entropion at baseline was the most significant predictor of recurrence of trichiasis at 3 years.

Conclusion: Trichiasis recurrence rates in the STAR trial remained low for up to 3 years following surgery. The protective effect of a single dose of azithromycin was less than at 1 year and, although not statistically significant, was still suggestive up to 3 years following trichiasis surgery.

Application to Clinical Practice: A single dose of azithromycin after surgery remains an integral component of the World Health Organization’s strategy for the elimination of trachoma by the year 2020.

Trial Registration: clinicaltrials.gov Identifier: NCT00347776.


Trachoma is the leading infectious cause of blindness, accounting for 15.5% of blindness worldwide. It is caused by infection with the bacterium Chlamydia trachomatis, with years of repeated infection leading to a chronic follicular conjunctivitis, which may result in scarring of the eyelid and turned lashes rubbing the globe. This condition, known as trachomatous trichiasis, may result in corneal scarring and eventual blindness. The World Health Organization (WHO) estimates that more than 6 million people are blind from trachoma. In regions where trachoma is hyperendemic, such as in Ethiopia, the prevalence of trichiasis in adults has been reported to be as high as 7%. The WHO has endorsed a multifaceted strategy for eliminating trachoma by the year 2020; this strategy consists of surgical correction of trichiasis, antibiotic use, facial cleanliness, and environmental improvement (SAFE). Bilamellar tarsal rotation is the current standard operation recommended by the WHO for correction of trichiasis because it has been shown to be more effective than electrolysis or cryoablation. However, trichiasis recurrence rates following surgery have been reported to be as high as 28% to 56% at 1 to 3 years in various studies. The specific objectives of our study were to determine the 3-year rates of trichiasis recurrence in this
Methods

The methods have been described in detail elsewhere. In summary, all patients with trichiasis who underwent surgery in the Wolayta Soddo Zone of southern Ethiopia between November 8 and December 30, 2002; between March 1 and May 10, 2003; and between October 8 and December 30, 2003, were screened for eligibility. Eligibility criteria included an age of 18 years or older, the presence of trichiasis in at least 1 eye, and no previous report of surgery for trichiasis in the study eye. The exclusion criteria were self-reported pregnancy, documented allergy to tetracycline, and plans to move out of the region within 1 year. If both eyes were eligible, the study eye was assigned according to the randomly assigned study arm. These subgroups have been combined into 1 group. The primary outcome, trichiasis recurrence in the study eye, was assessed at 2 weeks, 1.5 months, 6 months, 12 months, 18 months, 24 months, and 36 months following surgery. All assessments were performed clinically by a trained trachoma grader; each assessment was standardized to the senior project ophthalmologist. Trichiasis was defined as the presence of 1 or more lashes touching the globe and/or evidence of epilation, as specified by WHO criteria. Entropion was graded as mild (all lash bases visible), moderate (some lash bases visible but others not), or severe (all lash bases not visible).

All participants who did not have trichiasis 1 year after surgery received azithromycin or topical tetracycline again. There was no national trachoma control program or mass drug administration campaign in the Wolayta Soddo Zone of southern Ethiopia during the 3-year follow-up period.

Data analyses were performed using Stata version 9.0 (StataCorp). To incorporate the period in which recurrence occurred, life-table estimates of survival (free of trichiasis recurrence) were used. The primary comparison was cumulative incidence rate of recurrence in the tetracycline arm compared with that in the azithromycin arm. The log-rank test was used to assess differences in rates between the tetracycline and azithromycin groups. The Cox proportional hazards model was used to evaluate risk factors and adjust for confounders in predicting recurrences.

All participants provided written consent for our study, following a detailed oral and written description of all study procedures given in the local language. All procedures were approved by the Johns Hopkins Medical Institutions' institutional review board and by the Ethiopian Science and Technology Committee's National Ethical Clearance Committee. The trial is registered at clinicaltrials.gov (NCT00347776).

Results

A total of 1452 participants were enrolled in the trial, with 484 in the tetracycline group and 968 in the azithromycin group. There was a slightly higher percentage of female patients in the tetracycline group than in the azithromycin group (80.6 vs 75.5%; ). Otherwise, study participants were similar between the 2 groups with respect to age, severity of entropion, and severity of trichiasis. Three integrated eye care workers performed more than 99% of the surgical procedures, operating on a similar percentage of patients in both the control and treatment groups. Surgeons 4 and 5 only performed 15 surgical procedures in total and thus were not included in the multivariate analyses.

At the 3-year follow-up, the retention rate was more than 90% in each group (Figure 1), with 46 patients lost to follow-up in the tetracycline group and 84 patients lost to follow-up in the azithromycin group. The patients who were randomly assigned to receive oral azithromycin had a longer time to trichiasis recurrence at all time points compared with the patients who were randomly assigned to receive topical tetracycline, although this difference was not

Table 1. Characteristics of 1452 STAR Trial Participants at Baseline by Randomization Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tetracycline Group, No. (%)</th>
<th>Azithromycin Group, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>48.0 (12.8)</td>
<td>49.3 (13.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Female</td>
<td>390 (60.6)</td>
<td>731 (75.5)</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Severity of entropion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>257 (53.1)</td>
<td>553 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>150 (31.0)</td>
<td>267 (27.6)</td>
<td>.31</td>
</tr>
<tr>
<td>Severe</td>
<td>77 (16.0)</td>
<td>148 (15.3)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of lashes touching the globe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>112 (23.1)</td>
<td>197 (20.4)</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>103 (21.4)</td>
<td>237 (24.5)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>97 (20.2)</td>
<td>182 (18.8)</td>
<td>.55</td>
</tr>
<tr>
<td>7-9</td>
<td>45 (9.4)</td>
<td>97 (10.0)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>125 (26.0)</td>
<td>255 (26.3)</td>
<td></td>
</tr>
<tr>
<td><strong>IECW (surgeon) code</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>248 (51.2)</td>
<td>461 (47.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>164 (33.9)</td>
<td>345 (36.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>66 (13.6)</td>
<td>153 (15.8)</td>
<td>.52</td>
</tr>
<tr>
<td>4</td>
<td>6 (1.2)</td>
<td>8 (0.8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IECW, integrated eye care worker; STAR, Surgery for Trichiasis, Antibiotics to Prevent Recurrence.

aData are missing for 4 individuals in the tetracycline group.
By 3 years (Figure 2). At 3 years, the incidence of recurrence was 10% in the azithromycin group vs 13% in the topical tetracycline group. In a univariate analysis, predictors of trichiasis recurrence at 3 years included older age (hazard ratio, 1.01 [95% CI, 1.00-1.03]) and severity of entropion prior to surgery (hazard ratio, 1.77 [95% CI, 1.20-2.53] for moderate entropion and 2.98 [95% CI, 2.03-4.38] for severe entropion) (Table 2). Male sex was associated with increased recurrence (hazard ratio, 1.37 [95% CI, 0.96-1.93]), as was surgeon 3 (hazard ratio, 1.49 [95% CI, 0.97-2.27]). The variables in the univariate analysis with $P < .10$ were included in the multivariate model. After adjusting for age, sex, surgeon, baseline severity of entropion, and the number of lashes touching the globe, treatment with azithromycin was protective against trichiasis recurrence compared with treatment with topical tetracycline, although this difference was not statistically significant (hazard ratio, 0.78 [95% CI, 0.56-1.07]) (Table 3). Only being a male patient and having severe entropion at baseline were associated with trichiasis at the 3-year follow-up.

**COMMENT**

Surgical correction of trichiasis is an integral part of the WHO effort to eliminate blindness from trachoma by the year 2020. However, recurrence rates following surgery for trichiasis have been reported to be disappointingly high. A 4-year prospective study in the Gambia found the rate of recurrence of trichiasis following posterior lamellar tarsal rotation to be 41% at 4 years, with the majority of recurrences occurring during the first 6 months after surgery. A study in Oman demonstrated that, at 3.1 years of follow-up, 61.8% of patients who underwent bilateral lamellar tarsal rotation had a recurrence of trichiasis. Early recurrence, defined as 0 to 3 months following surgery, is thought to be due to surgical factors such as specific technique, whereas late recurrence is thought to be due to progressive scarring. The reported risk factors for recurrent trichiasis are tarsal conjunctival inflammation and...
Patients who did not have a recurrence of trichiasis by 1 year were treated again with either azithromycin or topical tetracycline, after the examination. Not everyone received the same drug as originally assigned, with 33% of those originally receiving azithromycin receiving topical tetracycline at 1 year and with 17% of those originally assigned to topical tetracycline receiving oral azithromycin. Thus, some of the low incidences of recurrence overall may be the result of patients receiving treatment again at 1 year, but we cannot ascertain the effect because everyone was treated again.

Analysis of the STAR trial data at 1 year demonstrated that infection with *Chlamydia trachomatis* after treatment was not a risk factor for recurrence of trichiasis following surgery. Data are not available for the 3-year end point because ocular swab specimens were not collected at the time. One reason that lower rates of *C. trachomatis* infection were not demonstrated in the azithromycin group compared with the tetracycline group may be that ocular swab specimens were only collected at 1.5 months and then at the point of trichiasis recurrence or at 12 months; thus, cases of infection in between these time points may not have been identified. In addition, the overall rates of infection were low, thus making it difficult to detect a difference between the groups. It is possible that treatment with azithromycin may play a role in preventing scar formation after surgery because anti-inflammatory effects have been described in the literature. However, studies have demonstrated that recurrence of trichiasis after surgery was highest in areas with the greatest prevalence of trachoma. It is not clear whether this is a result of persistent infection vs reinfection after surgery, and therefore this issue of recurrence requires further investigation.

In our study, the single dose of azithromycin administered was observed, and thus compliance was 100%. With the tetracycline group, only the first application of ointment was observed, and data on compliance for the next 6 weeks were not collected. It is possible that increased compliance in the azithromycin group may have contributed to the superior effect of azithromycin demonstrated in our trial. However, this advantage would also be applicable in a real-world setting because compliance with a single dose of oral azithromycin would be easier than compliance with a twice daily application of ointment for 6 weeks. In addition, although the cost of oral azithromycin is greater than the cost of topical tetracycline ointment ($4.60 vs $0.35 per child), oral azithromycin is readily available in sub-Saharan Africa through mass donation programs.

In conclusion, a single dose of oral azithromycin after surgery has been shown to be superior to topical tetracycline in protecting against the recurrence of trichiasis for up to 1 year, and some evidence is presented suggesting that the protective effect is evident for up to 3 years after surgery for trichiasis. Treatment with azithromycin thus remains an important component of the SAFE strategy for the eradication of trachoma.

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Correspondence: Sheila K. West, PhD, Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Room 129, Johns Hopkins University, 600 N Wolfe St, Baltimore, MD 21287 (shwest@jhmi.edu).

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REFERENCES


