Fluorometholone 0.1% as Ancillary Therapy for Trachomatous Trichiasis Surgery: Randomized Clinical Trial

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• PURPOSE: To assess the hypothesis that fluorometholone 0.1% eye drops are safe and effective as adjunctive therapy for trachomatous trichiasis (TT) surgery; determining the most promising dose.

• DESIGN: Randomized, placebo-controlled, double-masked parallel dose–ranging clinical trial.

• METHODS: Patients undergoing upper lid TT surgery at a rural Ethiopian hospital were randomized to fluorometholone 0.1% twice daily for 4 weeks, 4 times daily for 4 weeks, 4 times daily for 8 weeks, or matching frequency placebo in a 3:1:3:1:3:1 ratio for 1 eye. Randomization was stratified by TT severity (1-4 vs ≥5 lashes touching the globe). Safety outcomes (intraocular pressure [IOP] elevation, cataract, and other dose-limiting toxicities) and postoperative TT incidence were assessed over 1 year.

• RESULTS: Subjects randomized were 39:13:39:13:38:13 in the respective groups, and 1 subject in the 8-weeks fluorometholone group was withdrawn. Of 154 subjects, 148 (96.1%) completed 1 year's follow-up. Among 76 eyes receiving fluorometholone 4 times daily, 1 developed IOP elevation ≥ 30 mm Hg (to 37 mm Hg) and 1 had an allergic reaction attributed to the study drug; each resolved upon drug cessation without sequelae. No cataract or other dose-limiting toxicity events occurred. Postoperative TT within 1 year occurred in 29.3% of placebo eyes vs 17.7%, 19.6%, and 23.2% among the respective fluorometholone groups ($P = .29$ comparing placebo vs all active treatments combined).

• CONCLUSIONS: The results suggest fluorometholone 0.1% is likely to be safe and efficacious to reduce postoperative TT following TT surgery, and 1 drop twice daily for 4 weeks is the most promising dose. Confirmation in a full-scale clinical trial is needed before programmatic implementation. (Am J Ophthalmol 2019;197:145–155. © 2018 Elsevier Inc. All rights reserved.)

TRACHOMA IS THE LEADING INFECTION-INITIATED cause of blindness in the world[1] and the second-leading cause of blindness in Ethiopia.[2] The World Health Organization has endorsed a 4-pronged strategy to avoid future trachoma blindness: Surgery for trichiasis (inturned eyelashes), Antibiotics, Facial cleanliness, and Environmental improvement.[3] Trachoma blindness is mediated by persistent and progressive ocular surface damage associated with clinical and pathologic signs of inflammation.[3] Trachomatous cicatrical entropion and/or trichiasis (TT) results from trachomatous scarring and contraction of the palpebral conjunctiva.[4] Trichiasis is an important effector of visual loss from trachoma,[5] causing mechanical damage to the corneal surface with corneal opacity.[5] TT can be reversed by lid rotation surgery (TT surgery).[4] Thus, TT surgery to relieve trichiasis is 1 of the 4 "SAFE" priority interventions, avoiding blindness and relieving chronic pain from trichiasis in those with TT.[3]

Unfortunately, an undesirably high recurrence rate following trichiasis surgery occurs in many programmatic settings, reducing the programmatic benefits of surgery. Reports of the incidence of recurrence of TT after TT surgery (postoperative TT) have been highly variable. Rajak and associates found recurrence proportions ranging from 16.4% to 65% in observational studies, with 9 out of 11 reports of currently recommended procedures having 25% or higher incidence of postoperative TT.[6] Better results have been obtained in clinical trials,[7–11] which often selected best-performing surgeons and provided intensive training.

Among reported risk factors for postoperative TT, ongoing inflammation during the perioperative period has

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TABLE 1. Eligibility Criteria for a Dose-Finding Randomized, Controlled Trial of 3 Alternative Doses of Fluorometholone 0.1% Versus Placebo in Eyes Undergoing a First Trachomatous Trichiasis Surgery

Inclusion Criteria[a]	
1.	Age 18 years or more
2.	Diagnosis with trachomatous trichiasis
3.	Plan for lid rotation surgery (bilamellar tarsal rotation) on at least 1 upper eyelid
4.	LOCS III cataract grading is level 3 or less for the nuclear cataract scale, and level 2 or less for the cortical cataract and posterior subcapsular cataract scales
5.	Intraocular pressure between 8 mm Hg and 20 mm Hg in the study eye
Exclusion Criteria[b]	
1.	Contraindications to the use of the test articles
2.	Known allergy or sensitivity to any medication used in this study, including the study medication or its components (eg, fluorometholone)
3.	Currently taking more than 2 ocular antihypertensive medications in the study eye (prior intraocular pressure–lowering surgery is acceptable; combinations of 2 agents such as Cosopt and Combigan are considered 2 medications)
4.	Glaucoma sufficiently advanced that an intraocular pressure spike potentially would put the patient at substantial risk of vision loss, per study ophthalmologist's judgment
5.	Nonphakic (ie, pseudophakic or aphakic) study eye (contralateral nonphakic eye is permitted)
6.	Other than trachoma, any active ocular infections (bacterial, viral, or fungal), or any active ocular inflammation (eg, scleritis, iritis)
7.	History or diagnosis of ocular herpes or presence of a corneal lesion of suspected herpetic origin; or a diagnosis or suspected diagnosis of ophthalmic mycobacterial infection in either eye
8.	Corneal or scleral thinning in either eye
9.	A severe/serious ocular pathology or medical condition that may preclude study completion
10.	Any condition for which it is anticipated that ocular or systemic corticosteroid therapy would be required
11.	Unwilling to discontinue use of contact lenses for the duration of the study (should the unusual circumstance of a trachomatous trichiasis patient who uses contact lenses be encountered)
12.	Any significant illness or condition that could, in the investigator's or sub-investigator's opinion, be expected to interfere with the study parameters or study conduct; or put the subject at significant risk
13.	For women of childbearing age, currently pregnant and/or breastfeeding, as obtained by self-report (because of concerns about the [programmatic] use of azithromycin in this setting)

LOCS III = Lens Opacities Classification System III.
[a]Subjects were eligible for the study if all of the listed criteria were met, and none of the exclusion criteria were met.
[b]Subjects were not eligible for the study if any of the listed exclusion criteria were present.

been noted frequently.[4,6,7,12,13] Ongoing inflammation in the setting of trachoma is associated with progressive conjunctival scarring[14] and is often is seen in persons with trachomatous trichiasis.[5,10–12,15–18] Such inflammation only rarely is associated with *Chlamydia trachomatis* infection[12,15,19]; the specific causes thereof are incompletely understood. Given that inflammation—whether induced by the trachoma disease process or by surgery itself—most likely contributes to progressive cicatrization leading to postoperative TT in a clinically important proportion of cases, we hypothesized that interruption of inflammation with perioperative anti-inflammatory therapy potentially could improve TT surgery outcomes.

Fluorometholone 0.1%, a low-cost generic drug approved in most countries (including Ethiopia) for the indication of ocular inflammation, has lower intraocular penetration than alternative corticosteroids,[20] with correspondingly little intraocular pressure (IOP)-raising effect, while still having favorable effects on conjunctival inflammation.[21,22] As a first step in the evaluation of a new and potentially cost-effective approach to improving TT surgery outcomes based on this hypothesis, we conducted a dose-finding randomized trial evaluating the safety and potential efficacy of 3 doses of perioperative topical anti-inflammatory therapy with fluorometholone 0.1% eye drops compared with placebo treatment and untreated contralateral eyes.

METHODS

THE STUDY WAS DESIGNED AS A RANDOMIZED, DOUBLE-masked, parallel dose–ranging clinical trial in which a total of up to 156 subjects undergoing trachomatous trichiasis surgery for the first time in the study eye (39 in each of 3 active treatment groups and 39 in aggregate among the 3 corresponding placebo groups) were enrolled and had the study eye treated with the alternative study treatments. If the second eye was undergoing surgery as well, routine treatment was used for the eye. The clinical trial's

objectives were to assess the safety, tolerability, and (preliminary) efficacy of potentially feasible dosages of fluorometholone 0.1% for the treatment of subjects with trachomatous trichiasis undergoing lid rotation surgery. Our intent was to use the results to determine whether there is a safe and potentially efficacious dose appropriate for future trials, within the overarching agenda of developing an approach to alleviating blinding trachoma by improving outcomes of trichiasis surgery suitable for widespread programmatic use in the context of the "SAFE" strategy of trachoma mitigation. Protocol modifications were minimal during the study, the main change being to collect data on second eyes partway through the study. There were no changes to eligibility criteria or outcomes for treated eyes. The trial (ClinicalTrials.gov identifier: NCT01949454) was approved (and approval was maintained during the study) by Ethiopian and U.S. institutional review boards (IRBs) governing the investigators, including the National Research Ethics and Review Committee of the Ethiopian Ministry of Science and Technology and the Food, Medicine, and Healthcare Administration and Control Authority (FMHACA), as well as University of Pennsylvania IRB #4.

• **RECRUITMENT:** In order to conduct a preliminary evaluation of the treatment in a relevant programmatic context similar to where it might be used subsequently, patients were recruited to the clinical trial from the existing TT surgery program of the Ethiopian charity Grarbet Tehadiso Mahber, conducting approximately 4000 surgeries per year in a highly endemic region of the Southern Nations, Nationalities and Peoples' Region of Ethiopia. Because evaluation of safety was a primary goal of the study, all candidates were screened by a trained ophthalmologist (L.H.) to make sure that they did not meet the safety exclusion criteria and had little or no cataract and hence could be studied for progression of cataract. Eligibility criteria for the trial are summarized in Table 1.

Patients were recruited between November 13, 2013 and May 6, 2015 from those scheduled to undergo TT surgery at Grarbet Hospital (Butajira, Ethiopia) by the study coordinator and TT surgeons participating in the study. Eligible subjects were enrolled and randomized 3:1:3:1:3:1 to the following groups: (1) fluorometholone 0.1% 1 drop twice daily for 4 weeks; (2) placebo 1 drop twice daily for 4 weeks; (3) fluorometholone 0.1% 1 drop 4 times daily for 4 weeks; (4) placebo 1 drop 4 times daily for 4 weeks; (5) fluorometholone 0.1% 1 drop 4 times daily for 8 weeks; or (6) placebo 1 drop 4 times daily for 8 weeks. If both eyes were undergoing lid rotation surgery and were eligible, 1 eye was selected randomly as the study eye. Screen failures were documented on a subject screening log.

The randomization schedule—prepared in advance by the study coordinating center using permuted blocks of sizes 12 or 24 from a random number sequence generated in Stata 12.1 (StataCorp, College Station, Texas, USA)—was designed to provide an equal number of subjects in each of the 3 active treatment and the placebo treatment groups (taking all 3 placebo arms in aggregate as 1 group equal in size to the active treatment groups for purposes of data analysis). Randomization was stratified based on severity of TT: 1-4 lashes touching the globe vs 5 or more lashes touching the globe. Enrolled patients were given the next treatment off the pregenerated treatment assignment table by a study pharmacist at Grarbet Hospital, who was the only person with access to the treatment assignment table at the hospital.

• **SELECTION OF DOSAGES AND TREATMENT:** The following dosages were evaluated: (1) fluorometholone 0.1% 1 drop twice daily for 4 weeks; (2) fluorometholone 0.1% 1 drop 4 times daily for 4 weeks; and (3) fluorometholone 0.1% 1 drop 4 times daily for 8 weeks.

Each of these dosing frequencies had a corresponding placebo with matching frequency (artificial tears). These doses were selected as covering a range of potentially effective dosages that would be simple to implement in a programmatic setting by avoiding complicated tapering dose schedules.

In order to double-mask the study, an investigational pharmacy at the University of Pennsylvania (Philadelphia, Pennsylvania, USA) purchased commercially available fluorometholone 0.1% and artificial tears and repackaged them under sterile conditions into identical packets of active and placebo study drug. The study drug was imported into Ethiopia by commercial airliner in cabin temperature with the approval of FMHACA and subsequently kept at room temperature (within the package insert range of 2-25 degrees Celsius). During the trial, study drug was dispensed by the masked Grarbet Hospital pharmacist based on randomized treatment assignment. Breaking of masking was not required during the trial.

Surgery was performed by the TT surgeons actively performing surgery who were experienced with the bilamellar tarsal rotation surgery used in the trial, as per World Health Organization recommendations in place during the period of the study.[23] Contralateral eyes were managed per routine; by surgeon preference, when contralateral eyes were to be operated, this was done using a Trabut procedure (with only a conjunctival incision), which was the primarily used procedure at the site at the time of the study. Oral azithromycin was given as part of the surgical program to participating subjects. Removal of silk sutures used as part of TT surgery was done at the day 14 visit.

The first study eye drop was given prior to surgery, and postoperatively the study drug was given according to the randomly assigned schedule.

• **FOLLOW-UP AND STUDY OUTCOMES:** Masked participants were evaluated by masked study personnel at Grarbet Hospital's Eye Clinic at baseline, postoperatively (baseline and postoperative evaluation typically were conducted on

TABLE 2. Visit Schedule for a Dose-Finding Randomized, Controlled Trial of 3 Alternative Doses of Fluorometholone 0.1% Versus Placebo in Eyes Undergoing a First Trachomatous Trichiasis Surgery

Assessments	Visit 1 Baseline	Visit 2 Surgery	Visit 3 2 Weeks	Visit 4 4 Weeks	Visit 5 8 Weeks	Visit 6 3 Months	Visit 7 12 Months
Timing/interval (days [D]) pre-/postsurgery (= D 0)	D −4 to 0	D 0	D 14 ± 4	D 28 ± 7	D 56 ± 14	D 90, +30 or −15	D 365 ± 60
Informed consent, demographics, randomization	X						
Medical and ophthalmic history	X					X	X
Visual acuity, lens assessment	X					X	X
Trachoma, trichiasis grading, IOP	X		X	X	X	X	X
Surgical details		X					
Medication review	X	X	X	X	X	X	X
Adverse event review		X	X	X	X	X	X
Subject exits study							X

IOP = intraocular pressure.

the same day, or rarely a few days apart, as permitted by the protocol), and on follow-up visits on approximately days 14, 28, 56, 90, and 365 after trichiasis surgery (Table 2). After completing the day 365 visit, all subjects exited the study. The International and Ethiopia Principal Investigators, Safety Officer, and the Data and Safety Monitoring Committee members were unmasked, but they had no contact with patients during the study.

Safety Assessments. Potential adverse effects of corticosteroid therapy were prospectively assessed, including IOP measurement by Goldmann applanation tonometry at all visits except immediately postoperatively after lid rotation surgery; and grading of the lens for cataract by the study ophthalmologist using the Lens Opacities Classification System III[24] at the baseline, day 90, and day 365 visits (each after training in the measurement process until acceptable reproducibility was obtained). Subjects also were queried regarding adverse events at every follow-up visit, all of which were reviewed by the study ophthalmologist (L.H., who determined whether the event likely was treatment-related) and the study safety officer (J.H.K.). Dose-limiting toxicity that required cessation of therapy was tracked prospectively. Routine visual acuity also was assessed using an illiterate visual acuity testing system using presenting refractive correction (if any) at baseline, 90 days, and 365 days.

Efficacy Assessments. Trichiasis status was assessed at each follow-up visit (as well as at baseline). The primary efficacy outcome of postoperative TT was determined from these observations based on whether or not 1 or more lashes was touching the globe in an eye previously operated for TT. Recurrent trichiasis was managed according to best medical judgment as implemented in the programmatic context, typically with reoperation or epilation (for mild cases, eg, 1 lash touching the conjunctiva) at the discretion of the masked programmatic ophthalmologist (L.H.).

Sample Size Considerations and Statistics. For this safety-oriented study, we concluded that a relatively large number of subjects were needed in comparison to a masked placebo (39 in each group) to detect a modest level of increase in excess risk (an excess risk of 10% or more, eg, 4 more cases out of 39), which we judged would be sufficient to deter further consideration of the study treatment. Interim analyses were conducted for presentation to the Data and Safety Monitoring Committee approximately annually, to assure safety in this safety-oriented trial. There were no prespecified stopping guidelines.

For statistical analysis, the safety population and the intention-to-treat population were defined as all subjects enrolled in the study. The maximum tolerable dose among the 3 doses studied was prespecified to be the highest dose at which ≤3 subjects more in the treatment group than the placebo group would have dose-limiting toxicity, cataract, or elevated IOP ≥ 30 mm Hg (at any visit). Survival analysis of time to postoperative TT was conducted using Cox proportional hazards models by treatment assignment and for comparison of active treatment to untreated eyes (including contralateral eyes). Descriptive statistics (cross-tabulation of dichotomous variables, bar graphs of numerical variables with standard deviation, stacked graphs of the distribution of multichotomous ordinal outcomes over time) were used to assess the occurrence of outcomes. Missing data were rare and were not imputed. *P* values given are nominal and 2-sided, given that the primary aims of the study were to assess safety based on counts of prespecified adverse events and assess benefits in a preliminary manner. All statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

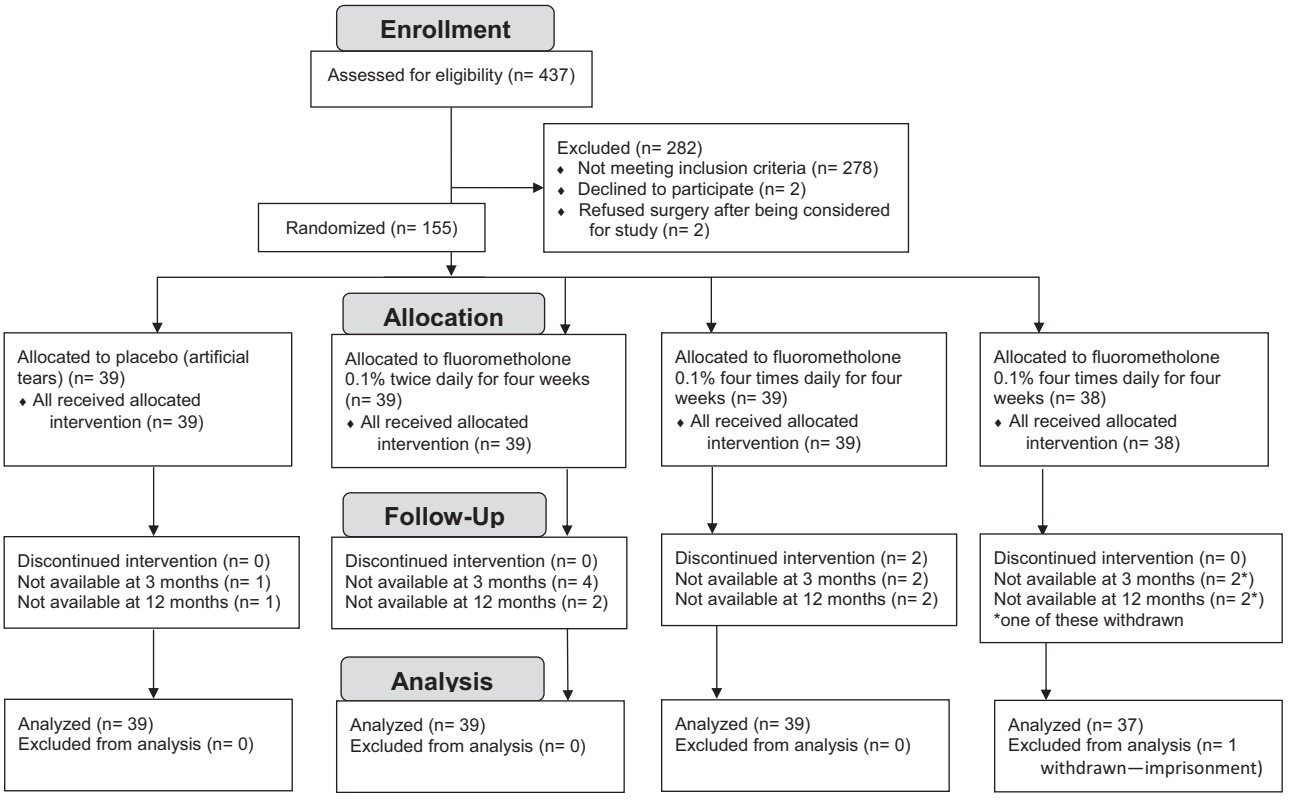


FIGURE 1. CONSORT diagram for participants in a dose-finding randomized, controlled trial of 3 alternative doses of fluorometholone 0.1% vs placebo in eyes undergoing a first trachomatous trichiasis surgery. Other than 1 patient administratively withdrawn owing to imprisonment, the only reason for failure to follow up was unavailability of a small number of patients to come for follow-up within the specified visit window. Adapted from http://www.consort-statement.org/consort-statement/flow-diagram (accessed August 20, 2018).

RESULTS

ONE HUNDRED FIFTY-FIVE EYES OF 155 PATIENTS WERE enrolled in the study between 2013 and 2015, randomized to the alternative fluorometholone 0.1% or placebo treatments (illustrated in CONSORT diagram, Figure 1), and received TT surgery. Enrollment was terminated at 155 on the recommendation of the Data and Safety Monitoring Committee in May 2015 for logistical reasons. One enrolled subject in the 4 times daily for 8 weeks group was withdrawn from the study subsequently at Institutional Review Board request owing to imprisonment. Ultimately 39, 39, and 38 were allocated to the twice daily, 4 times daily for 4 weeks, and 4 times daily for 8 weeks fluorometholone groups, and 13 to each corresponding-frequency placebo group (39 altogether). Among the patients, 147 (94.8%) and 148 (95.5%), respectively, completed the 3- and 12-month follow-up visits. Participants used the study treatments except when they had to be stopped (see below). Bottles inspected at follow-up visits were found to be partially used.

The characteristics of the randomized treatment groups are given in Table 3. There were modest but statistically significant differences among the groups by age (overall $P = .034$), with the aggregated placebo group being the youngest (mean = 34.4 years, standard deviation 10.3 years). Bilaterality of trichiasis tended to be more frequent in the active treatment groups, but not to a statistically significant degree (overall $P = .08$), with the placebo group having the least bilateral trichiasis (59.0%) and the active treatment groups having more bilaterality (74.4% 84.6%). Otherwise, remarkable or statistically significant differences did not exist between the treatment groups (all $P > .10$). In each of the groups, about half had between 1 and 5 lashes touching the globe in the study eye, and about half had more (most of these eyes had 10 or more lashes touching). In addition, about half of study eyes had evidence of recent epilation at baseline. Follicular trachoma and intense trachomatous inflammation were not observed in any of the study eyes. Extensive trachomatous scarring of the superior palpebral conjunctiva was visible in about two thirds of study eyes at baseline.

• **SAFETY OUTCOMES:** No immediate problems of surgery were reported for any of the study eyes, nor did any patient report tolerability problems for the study treatments.

TABLE 3. Baseline Characteristics by Treatment Group for a Dose-Finding Randomized, Controlled Trial of 3 Alternative Doses of Fluorometholone 0.1% Versus Placebo in Eyes Undergoing a First Trachomatous Trichiasis Surgery

Characteristic	By Treatment Group					
	Placebo	2×/4 wk	4×/4 wk	4×/8 wk	*P*	Total
Age (y), mean (SD)	34.4 (10.3)	37.7 (11.1)	41.7 (12.3)	37.8 (10.0)	.034	37.9 (11.2)
Sex						
Female	33 (84.6%)	29 (74.4%)	29 (74.4%)	28 (75.7%)	.65	119 (77.3%)
Male	6 (15.4%)	10 (25.6%)	10 (25.6%)	9 (24.3%)		35 (22.7%)
Bilaterality of TT						
Unilateral	11 (28.2%)	9 (23.1%)	6 (15.4%)	7 (18.9%)	.55	33 (21.4%)
Bilateral	28 (71.8%)	30 (76.9%)	33 (84.6%)	30 (81.1%)		121 (78.6%)
Study eye visual acuity (logMAR)						
Below median VA	22 (57.9%)	19 (48.7%)	14 (35.9%)	18 (50.0%)	.28	73 (48.0%)
Median or above VA	16 (42.1%)	20 (51.3%)	25 (64.1%)	18 (50.0%)		79 (52.0%)
Medical history						
≤20%	38 (100.0%)	33 (100.0%)	36 (100.0%)	33 (97.1%)	.37	140 (99.3%)
>20%	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)		1 (0.7%)
Number of nonstudy medications						
0	39 (100.0%)	37 (94.9%)	35 (89.7%)	37 (100.0%)	.23	148 (96.1%)
1	0 (0.0%)	1 (2.6%)	3 (7.7%)	0 (0.0%)		4 (2.6%)
2	0 (0.0%)	1 (2.6%)	1 (2.6%)	0 (0.0%)		2 (1.3%)
Any prior ocular surgery						
No	33 (86.8%)	30 (90.9%)	35 (97.2%)	33 (97.1%)	.24	131 (92.9%)
Yes	5 (13.2%)	3 (9.1%)	1 (2.8%)	1 (2.9%)		10 (7.1%)
Number of lashes touching the cornea, mean (SD)	6.0 (3.3)	5.9 (3.7)	4.9 (3.4)	5.3 (3.5)	.45	5.5 (3.5)
Lashes touching globe						
Mild (1-5)	17 (43.6%)	20 (51.3%)	23 (59.0%)	21 (56.8%)	.34	81 (52.6%)
Major (6-9)	8 (20.5%)	2 (5.1%)	5 (12.8%)	3 (8.1%)		18 (11.7%)
Severe (10+)	14 (35.9%)	17 (43.6%)	11 (28.2%)	13 (35.1%)		55 (35.7%)
Lashes touching the cornea	39 (100.0%)	39 (100.0%)	39 (100.0%)	37 (100.0%)	.	154 (100.0%)
Evidence of epilation						
No	17 (43.6%)	20 (51.3%)	16 (41.0%)	15 (40.5%)	.76	68 (44.2%)
Yes	22 (56.4%)	19 (48.7%)	23 (59.0%)	22 (59.5%)		86 (55.8%)
Area of entropion >50%						
No	7 (17.9%)	13 (33.3%)	9 (23.1%)	4 (10.8%)	.11	33 (21.4%)
Yes	32 (82.1%)	26 (66.7%)	30 (76.9%)	33 (89.2%)		121 (78.6%)
Study eye trachomatous inflammation, follicular: No	36 (100.0%)	35 (100.0%)	37 (100.0%)	33 (100.0%)	.	141 (100.0%)
Study eye trachomatous inflammation, intense: No	36 (100.0%)	35 (100.0%)	37 (100.0%)	33 (100.0%)	.	141 (100.0%)
Study eye trachomatous scarring						
No	10 (27.8%)	14 (38.9%)	13 (35.1%)	12 (36.4%)	.78	49 (34.5%)
Yes	26 (72.2%)	22 (61.1%)	24 (64.9%)	21 (63.6%)		93 (65.5%)
Study eye corneal opacity						
No	32 (88.9%)	31 (86.1%)	34 (91.9%)	30 (90.9%)	.86	127 (89.4%)
Yes	4 (11.1%)	5 (13.9%)	3 (8.1%)	3 (9.1%)		15 (10.6%)
Any problem reported with surgery: No	39 (100.0%)	39 (100.0%)	39 (100.0%)	37 (100.0%)	.	154 (100.0%)

TT = trachomatous trichiasis; VA = visual acuity.

Regarding IOP outcomes, 1 eye in the fluorometholone 0.1% 1 drop 4 times daily for 4 weeks group was noted to have elevated IOP at the 2-week study visit to a level of 37 mm Hg (Figure 2). Study treatment was suspended for this eye (without unmasking) and timolol 0.5% prescribed for 2 weeks. Thereafter, timolol 0.5% was stopped, and the IOP remained normal throughout the remaining follow-up. At 1 year, the cup-to-disc ratio (0.2) remained the same as at baseline for this eye. Taking the 2 treatment groups receiving 4 drops of

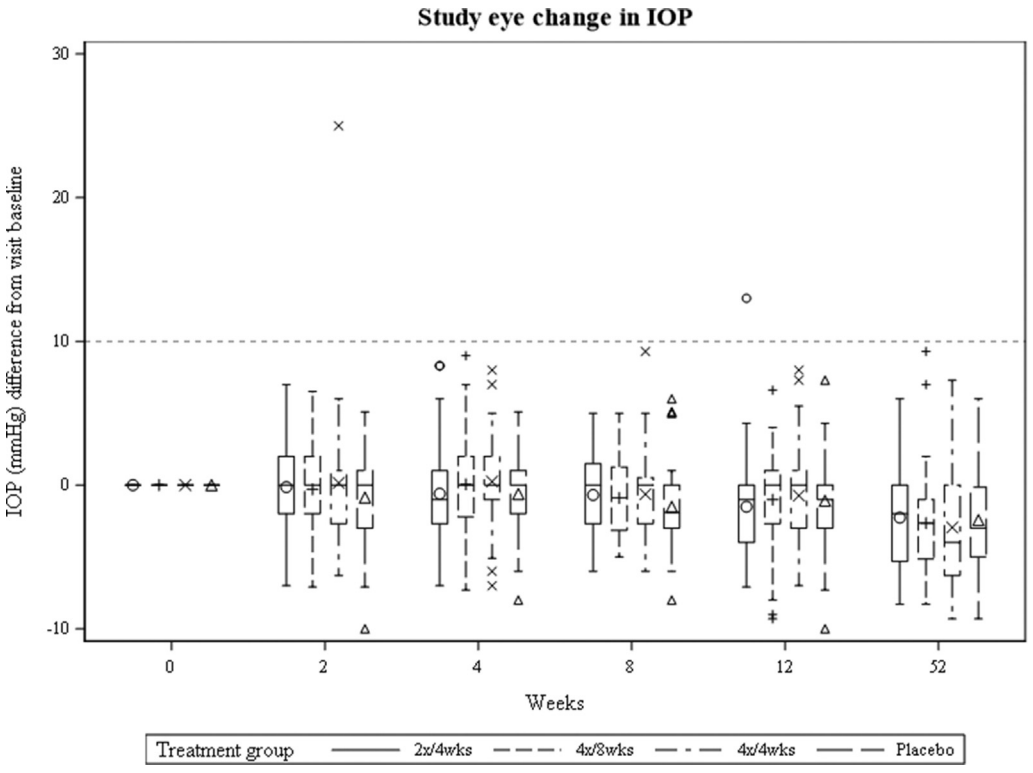


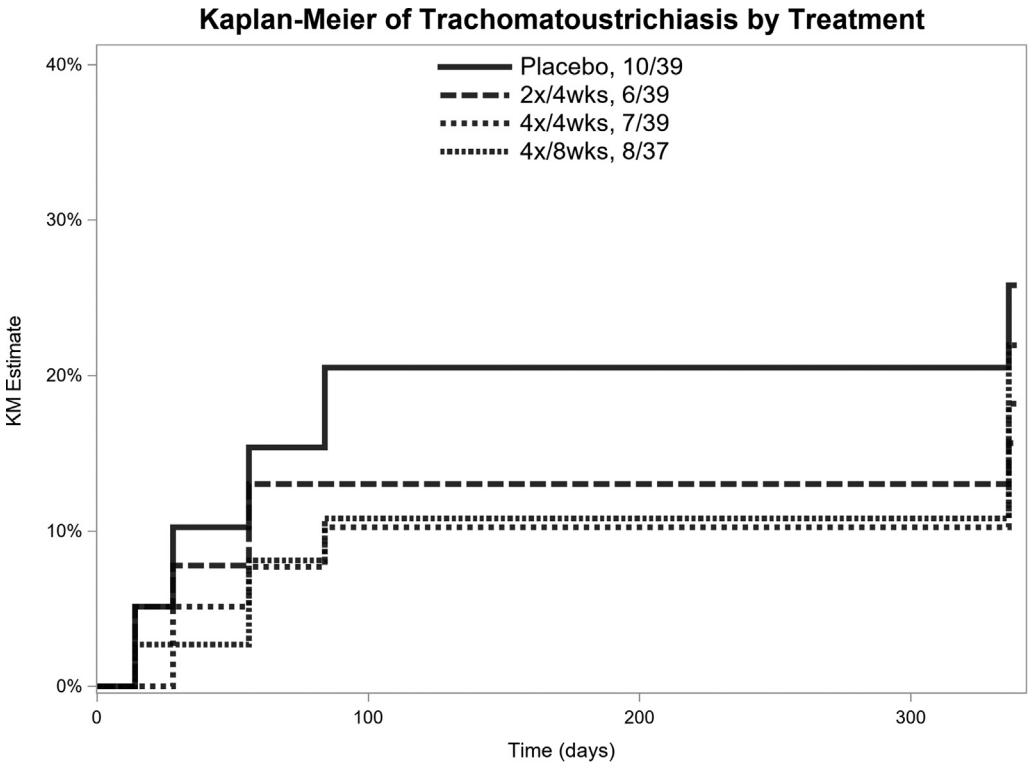
FIGURE 2. Changes in intraocular pressure (IOP) among eyes of participants in a dose-finding randomized, controlled trial of 3 alternative doses of fluorometholone 0.1% vs placebo in eyes undergoing a first trachomatous trichiasis surgery. 2×/4wks = fluorometholone 0.1% 1 drop 2 times daily for 4 weeks; 4×/4wks = fluorometholone 0.1% 1 drop 4 times daily for 4 weeks; 4×/8wks = fluorometholone 0.1% 1 drop 4 times daily for 4 weeks; Placebo = masked treatment with artificial tears at equal frequencies to the active treatment groups (one third each).

fluorometholone 0.1% daily together, the proportion developing an IOP elevation ≥ 10 mm Hg higher than baseline (1/76) was 1.3% (95% confidence interval [CI]: 0.03%–7.1%). No other IOP elevations ≥ 30 mm Hg were observed in the 2 drops per day fluorometholone 0.1% group (0/39) nor in the aggregated placebo group (0/39) (97.5% 1-sided CI for each: up to 9.0%) during study treatment. One eye in the twice-daily fluorometholone group developed a ≥10 mm Hg rise in IOP from baseline at the 3-month visit (2 months after completion of study treatment). This eye had a baseline IOP of 8 mm Hg, IOP of 15 mm Hg and 14 mm Hg during treatment, IOP of 21 mm Hg at 3 months, and IOP of 14 mm Hg at 12 months (without any IOP-lowering treatment).

Regarding cataract outcomes, no instances of the prespecified outcome of a Lens Opacities Classification System III 2-unit rise in nuclear opacity, nuclear color, cortical cataract, or posterior subcapsular cataract were observed in any of the groups (details provided in Supplement 1; Supplemental Material available at AJO.com). The distributions of lens gradings at both 3 and 12 months were similar to baseline, with neither any tendency observed toward increased cataract in any group nor any remarkable difference between groups.

Other dose-limiting toxicity was observed in only 1 instance: 1 eye in the fluorometholone 4 times daily for 4 weeks group developed an allergic reaction. The symptoms of medication allergy resolved promptly with suspension of study treatment. Taking all 4-drops-per-day fluorometholone-treated eyes together and counting the case of IOP elevation and the case of allergy together, the incidence of dose-limiting toxicity was 2 in 76 (2.6%; 95% CI: 0.3%–9.1%). No dose-limiting toxicity was observed in the 2-drops-daily group (upper limit of 97.5% 1-sided confidence interval: 9.0%).

A total of 128 adverse events were reported during the trial (details provided in Supplement 2; Supplemental Material available at AJO.com). The most common adverse events were upper lid or lower lid TT. Blepharitis requiring prescription treatment was diagnosed in 15 study eyes (vs 12 contralateral eyes), 6 in the placebo group (15%) and 2 (5.1%), 4 (10%), and 3 (8.1%), respectively, in the twice daily, 4 times daily for 4 weeks, and 4 times daily for 8 weeks treatment groups. Granuloma was observed in 6 study eyes and 4 contralateral eyes, with 1 or 2 granulomas in each as-randomized treatment group. Conjunctivitis was observed in 2 study eyes (both in the placebo group) and 5 contralateral eyes; no cases were



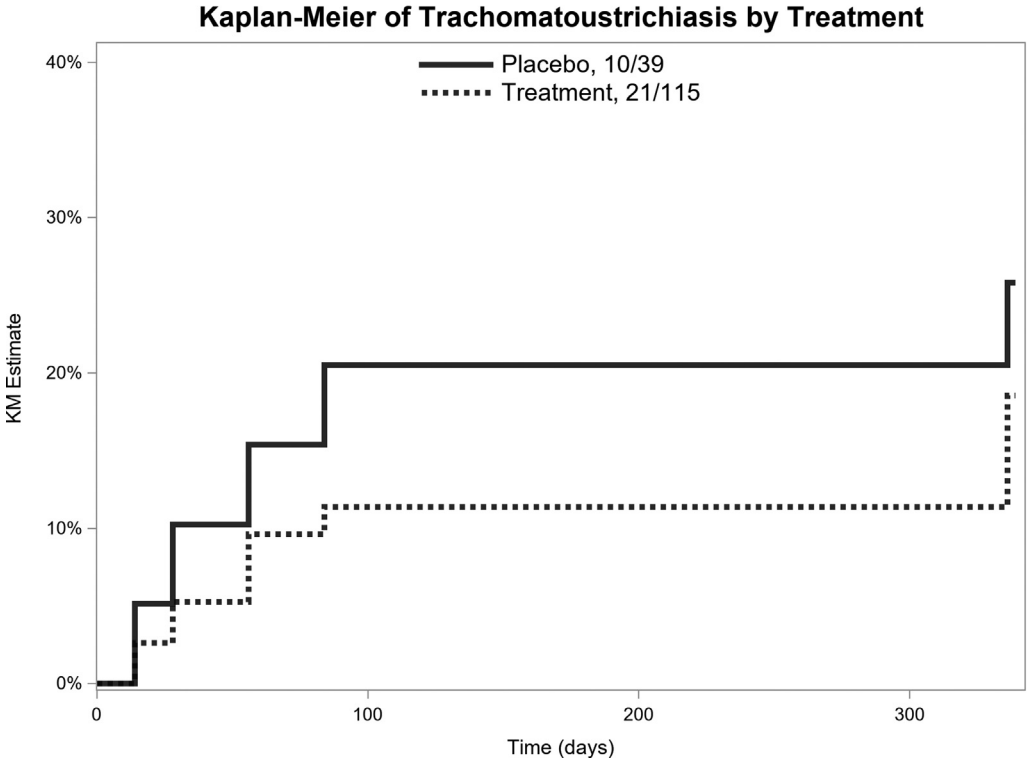


FIGURE 3. (Top) Incidence of postoperative trachomatous trichiasis (TT) by treatment assignment. (Bottom) Incidence of postoperative TT by placebo vs all active treatments combined. Each among eyes of participants in a dose-finding randomized, controlled trial of 3 alternative doses of fluorometholone 0.1% vs placebo in eyes undergoing a first TT surgery.

observed in fluorometholone treatment–assigned eyes (Fisher exact test comparison between active treatment and placebo, $P = .06$; for active treatment vs a combination of placebo and contralateral eyes, $P = .016$).

Regarding infectious adverse events, 1 eye in the 4 times daily for 4 weeks flurometholone group was observed to have punctate epithelial erosions while under treatment; these were suspected of being herpetic by the masked study ophthalmologist, and they resolved without sequelae following treatment with antiherpetic medication (without discontinuation of study treatment). One study eyelid each in the placebo and the fluorometholone 4 times daily for 8 weeks group were diagnosed with a wound infection; the former resolved after a long clinical course requiring reoperation, whereas the latter resolved promptly with antibiotics alone. One contralateral eyelid developed a wound infection as well, which resolved with suture removal and antibiotics. One placebo-treated eye developed ipsilateral dacryocystitis (successfully managed with antibiotics), and 1 contralateral eye in the twice daily for 4 weeks fluorometholone group developed a canalicular obstruction. Conjunctivitis (see above) may have been infectious in some instances. No other ocular infectious adverse events were observed.

• **EFFICACY OUTCOMES:** Postoperative TT was observed in 31 study eyes overall by 12 months, with the following Kaplan-Meier estimates of the proportion recurrent by 1 year: $_{16.5}29.3\%_{48.7}$ in the placebo group (95% CI indicated by subscripts before and after percentages), vs $_{8.1}17.7\%_{36.1}$, $_{9.9}19.6\%_{36.7}$, and $_{12.6}23.2\%_{40.6}$ in the twice daily for 4 weeks, 4 times daily for 4 weeks, and 4 times daily for 8 weeks fluorometholone groups (Figure 3, Top, overall $P = .70$). Contralateral eyes (which received routine surgery without fluorometholone or placebo) had $_{21.2}31.3\%_{44.6}$ postoperative TT within 12 months, similar to the placebo group. All treated eyes combined had $_{13.6}20.2\%_{29.3}$ postoperative TT within 12 months compared to 29.3% in placebo eyes (Figure 3, Bottom, $P = .29$). In most instances, postoperative TT was less severe than preoperative TT; the masked study ophthalmologist decided whether postoperative TT required additional surgery. A post hoc table analysis comparing the proportion of placebo eyes receiving reoperation (7/39 = 18%) vs the proportion of active treatment eyes requiring reoperation (7/122 = 5.7%) demonstrated a significantly lower incidence of reoperation in the combined active treatment groups ($P = .018$).

DISCUSSION

IN THIS 1-YEAR RANDOMIZED, CONTROLLED, MASKED CLINical trial following 154 patients after upper lid TT surgery, perioperative and early postoperative treatment with fluorometholone 0.1% in comparison with placebo and untreated contralateral eyes was associated with minimal adverse effects and a preliminary suggestion of efficacy. Tolerability was favorable for the study treatment, with no problems observed.

Among the prespecified adverse outcomes studied—elevation of IOP, cataract, and dose-limiting toxicity—events were rare, suggesting that the use of fluorometholone at a programmatic level would be unlikely to incur a substantial number of clinically important side effects. Based on theoretical considerations, we anticipate that the twice-daily dosing should be slightly more favorable in terms of adverse outcome risk. The risk of nonprespecified adverse outcomes, such as blepharitis, granuloma, and conjunctivitis, appears to have been no worse in the active treatment groups than in the placebo group; that conjunctivitis never was diagnosed in fluorometholone-assigned eyes provides modest support of our rationale that the treatment would be effective in averting postoperative conjunctival inflammation. A large-scale clinical trial could confirm these conclusions more definitively.

Regarding efficacy, the study was designed to conduct a preliminary assessment thereof, and the primary efficacy results are not statistically significant, as anticipated. However, the consistency of reduction of incident postoperative TT by about one third across treatment groups compared to placebo and contralateral eyes, and the significantly lower need for reoperation with fluoreometholone in a post hoc comparison, suggest that fluorometholone may be efficacious in reducing the incidence of postoperative TT. Efficacy of fluorometholone also would be consistent with prior clinical[5,10–12,14–18] and mechanistic research,[15,25] which has indicated the importance of inflammation in trachomatous scarring. However, given that corticosteroids have a broad spectrum of anti-inflammatory effects, our results do not provide strong evidence about which inflammatory pathways are most important in the pathogenesis of postoperative TT.

The primary limitation of the study is that it was designed as a phase 2–like safety and dose-finding study without sufficient statistical power to definitively establish safety and efficacy. A full-scale confirmatory trial will be needed to establish whether fluorometholone should be used on a programmatic basis for TT surgery programs. Also, we report results of bilamellar tarsal rotation (BTR) surgery in study eyes based on World Health Organization recommendations in place at the time of the study's commencement, whereas many programs use the Trabut procedure, which subsequently has been shown to have at least as good results as BTR in a randomized clinical trial,[9] and now is accepted along with BTR as a recommended approach to TT surgery by the World Health Organization.[3] However, given that any effects of fluorometholone on the conjunctival surgical incision ought to apply to

both surgical procedures (whereas topical fluorometholone is not applied to the eyelid incision of BTR), and that any effects on ongoing trachomatous inflammation should apply equally with both procedures, it seems likely that results should be similar across the 2 procedures.

In summary, the results of this preliminary trial suggest that fluorometholone 0.1% is reasonably safe and likely to be efficacious as adjunctive treatment along with TT surgery. The anticipated minimal risk and efficacy of such treatment ought to be confirmed in a large-scale field trial prior to adoption of the treatment. A possible advantage in observed adverse effect outcomes, theoretical considerations, and similar efficacy observations in this trial suggest that the twice-daily dosage of fluorometholone 0.1% is the most promising dose for further study. Given the potential for a programmatically/clinically important reduction in difficult-to-manage postoperative TT, a definitive clinical trial evaluating the use of fluorometholone as adjunctive therapy for TT surgery seems justified.

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