The Impact of Topical Corticosteroid Use before Diagnosis on the Outcome of Acanthamoeba Keratitis

Dana Robaei, PhD, FRANZCO,[2] *Nicole Carnt, B.Optom, PhD,*[2]
Darwin C. Minassian, FRCOphth, MSc(Epidem),[3] *John K. G. Dart, MD, FRCOphth*[1]

Objective: To examine the impact of topical corticosteroid use before the diagnosis of Acanthamoeba keratitis (AK) on final visual outcomes and to determine the prognostic factors predicting poorer outcomes.

Design: Cohort study.

Participants: A total of 209 eyes of 196 patients with retrievable medical records, diagnosed with AK at Moorfields Eye Hospital, London, between January 1991 and April 2012. One eye was randomly excluded from analysis in the 13 cases of bilateral AK.

Methods: Patient demographic, initial clinical examination findings, and management details were collected. The outcomes of patients treated with topical corticosteroids before diagnosis of AK were compared with those not treated with topical corticosteroids before diagnosis. A multivariable logistic model, optimized for prior corticosteroid use, was used to derive the odds ratios (ORs) of a suboptimal visual outcome.

Main Outcome Measures: Suboptimal visual outcome was defined as final visual acuity (VA) $\leq$20/80, corneal perforation, or need for keratoplasty.

Results: Acanthamoeba keratitis was diagnosed on microbiological culture in 94 eyes (48.0%), on histopathologic examination in 27 eyes (13.8%), on confocal microscopy in 38 eyes (19.4%), and on the basis of a typical clinical course and response to treatment in 37 eyes (18.9%). Final VA and prior corticosteroid use data were available for 174 eyes (88.8%). In multivariable analysis, corticosteroid use before diagnosis was associated with suboptimal visual outcome (OR, 3.90; 95% confidence interval [CI], 1.78−8.55), as were disease stage 3 at presentation (OR, 5.62; 95% CI, 1.59−19.80) and older age (60+ years) at diagnosis (OR, 8.97; 95% CI, 2.13−37.79).

Conclusions: Corticosteroid use before diagnosis of AK is highly predictive of a poorer visual outcome. This is largely due to the initial misdiagnosis of AK as herpetic keratitis. It is important to include AK in the differential diagnosis of keratitis in all contact lens users with keratitis, particularly before making a diagnosis of herpes keratitis and before the use of topical corticosteroids in the therapy of any indolent keratitis. *Ophthalmology 2014;■:1−6 © 2014 by the American Academy of Ophthalmology.*

Acanthamoeba keratitis (AK) is an uncommon but severe corneal infection. Since the first report of AK in the literature in 1974,[1] there have been improvements in diagnosis and treatment,[2,3] although many patients still experience significant morbidity and visual impairment.[4]

The role of topical corticosteroids in the management of AK remains controversial.[5,6] Although some advocate their use for severe corneal inflammation, neovascularization, and the management of scleritis,[7] others believe that they potentiate infection and result in a poorer outcome.[8] However, more than 70% of ophthalmologists experienced in managing AK use topical corticosteroids for management.[9]

Likewise, little is known about the impact of topical corticosteroid use before the diagnosis of AK. Although this practice has been widely reported, because of an initial misdiagnosis of AK, usually as herpes keratitis, its impact on final visual outcomes has been uncertain[10−13] in the relatively small case series in which this has been evaluated. These studies may have been underpowered to demonstrate an effect and were not optimized to assess this exposure. Both the misdiagnosis and the use of corticosteroid, before the use of anti-amoebic therapy, are avoidable. If the latter results in poorer outcomes, this is important knowledge, which should alter clinicians' approach to the diagnosis and treatment of keratitis, hence the rationale for the investigation reported. The purpose of this study is to define the impact of topical corticosteroid use before diagnosis on visual outcomes in AK.

Methods

Case Ascertainment

A retrospective review of the medical records of patients diagnosed with AK at Moorfields Eye Hospital between January 1991 and April 2012, and with retrievable medical records, was conducted. These cases were identified from our current microbiology laboratory electronic database, which started in the year 2000. An additional 9 cases from a previous database also were included. The study was approved by the Moorfields Eye Hospital Clinical

ISSN 0161-6420/14/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2014.01.031

Research Management and Audit Department, and the Tenets of the Declaration of Helsinki were adhered to.

Cases were included in the analyses if they had a positive *Acanthamoeba* culture or histopathologic confirmation of trophozoites or cysts. Culture-negative cases that were positively identified as having *Acanthamoeba* cysts on confocal microscopy together with a typical clinical course and response to treatment were included. In the absence of the conditions described, patients with perineural corneal infiltrates or a typical clinical course with a response to anti-amoebic treatment were included in the sample.

One eye only of each bilateral case was selected randomly for inclusion in the analysis, by sequential reference to a table of random numbers, using the rule "right eye if random number is even, otherwise left eye."

Exposure of Primary Interest

Patients were classified into 2 main comparison cohorts according to topical corticosteroid use before diagnosis: Those treated with prior corticosteroids formed the exposed cohort, and those with no prior corticosteroids formed the unexposed cohort.

Definition of Visual Outcomes

Our primary outcome measure was a suboptimal visual outcome, defined as a final best-available visual acuity (VA) $\leq$20/80 (recorded after completion of therapy for the AK episode), corneal perforation, or need for keratoplasty.

Definition of Disease Staging

Disease stage at presentation was divided into 3 categories: Stage 1 AK was defined as the presence of corneal epitheliopathy only. Stage 2 AK was defined by the presence of $\geq$1 corneal epithelial defects, perineural infiltrate, or stromal infiltrate in addition to stage 1 findings. Stage 3 disease required the presence of a corneal ring infiltrate and 1 or more features of stage 2 disease.

Statistical Analyses

Statistical analyses were performed using Stata software version 8 (StataCorp LP, College Station, TX). Analysis of the impact of corticosteroid use on final visual outcomes was restricted to those with available corticosteroid use and final VA data. Patients with significant preexisting disease-limiting visual potential also were excluded.

Univariable Analyses

The frequency of demographic and clinical factors in the 2 exposure groups of primary interest (exposed and not exposed to topical corticosteroids before diagnosis) was estimated, using exact procedures for computation of 95% confidence intervals (CIs). The "crude" association of the exposure of primary interest with other exposures (one at a time) also was examined, using the Fisher exact test for comparison of frequencies and the nonparametric 2-sample Wilcoxon rank-sum (Mann–Whitney) test for comparison of means or medians.

Multivariable Analyses

Logistic regression models were used to assess the effect of exposures on the visual outcome. The exposure of main interest was topical corticosteroid use before diagnosis, all others being considered as auxiliary variables (potential confounders/effect modifiers). Preliminary cross-tabulations examining the interrelations of the visual outcome with exposures helped to identify auxiliary variables that could be effect modifiers or important confounders, thus candidates for inclusion in the logistic models.

The modeling process was designed to arrive at a final logistic model that estimated the odds ratio (OR) for the exposure of main interest, with optimal control of confounding effects. Auxiliary variables included in the final model were those suspected or known a priori to be associated with the outcome and with the exposure of main interest. Also included were the auxiliaries identified in the modeling process as important confounders on statistical grounds. Events that were believed to have occurred as a consequence of prior corticosteroid use and that could increase the risk of a suboptimal outcome were not adjusted for, because doing so would lead to underestimation of the prior corticosteroid effect. Likelihood ratio tests were used to assess effect modification by auxiliary variables. Model performance and validity were assessed through post-fit diagnostics.

Results

A total of 196 patients diagnosed with AK between 1991 and 2012 were included. Thirteen patients (6.6%) had bilateral infection, and in this group, 1 eye was randomly excluded from further analysis, leaving 196 eyes of 196 patients. The majority of patients were treated with dual therapy using a biguanide (polyhexanide 0.02, 0.06% or chlorhexidine 0.02, 0.2%) and diamidine (propamidine 0.1% or hexamidine 0.1%). Table 1 outlines the primary criteria for AK diagnosis in all patients and shows the numbers (n = 22) excluded from analysis because of missing data on prior corticosteroid use or on the primary outcome, leaving a total of 174 patients for further analysis. Of these, 87 (50%) had topical corticosteroids before diagnosis of AK.

Table 2 compares the demographic factors between those exposed and unexposed to prior corticosteroids. Patients who had received steroids before the diagnosis of AK were significantly younger (mean, 33.6 years) than those who had not (mean, 40.3 years; $P<0.005$), had significantly more visits to the clinic

Table 1. Acanthamoeba Keratitis Case Ascertainment (n = 196)

Basis of Diagnosis	n (%)	Excluded from Analysis n = 22	
		Missing Data on Prior Corticosteroid Use	*Outcome Not Ascertained Because of Preexisting Eye Disease*
Positive culture (i.e., corneal scrape positive)	94 (48.0)	5	2
Positive histopathology	27 (13.8)	4	0
Positive confocal microscopy and typical clinical course	38 (19.4)	2	5
Perineural infiltrates and typical clinical course	20 (10.2)	1	1
None of the above: typical clinical course only	17 (8.7)	1	1
Total	196 (100)	13	9