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Topical Corticosteroids in the Management of Bacterial Keratitis

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Abstract

Bacterial keratitis can cause significant morbidity from ulceration of the cornea and the resultant scarring. The use of steroids to decrease these complications is controversial with arguments for and against their use. The SCUT (Steroids for Corneal Ulcers Trial) was initiated in 2006 to definitively determine whether steroids in bacterial keratitis were beneficial or harmful. While the SCUT showed no benefit or harm overall, subgroup analyses showed that larger, more central ulcers with very poor initial visual acuity may benefit. On the other hand, Nocardia ulcers that were treated with steroids had worse outcomes. The study did have some limitations as the patient population was not typical for bacterial keratitis in the United States, and there were some criticisms of the therapeutic approach so the question is still not definitively answered.

Keywords

Steroids; corticosteroids; bacterial keratitis; corneal ulcer; ulceration; inflammation; scarring; perforation; cytokines

Introduction

Bacterial keratitis is a medical emergency with an incidence ranging from approximately 10 per 10,000 in tropical and developing nations to 10 per 100,000 in more temperate climates in developed nations.[1–5] The major morbidity from infectious keratitis is from corneal ulceration and perforations which can result in vision loss from the resultant endophthalmitis or severe scarring and vascularization.[6] Even with appropriate treatment, there is a high incidence of visual loss due to the development of corneal scarring. The cause of this scarring is from a combination of corneal and inflammatory factors. In infectious keratitis, a cascade of inflammation is triggered by bacterial invasion. This results in the influx of inflammatory cells into the infected area with release of inflammatory cytokines, collagenases, and growth factors such as Transforming Growth Factor-beta (TGF-β) and Connective Tissue Growth Factor (CTGF) from the injured epithelial and stromal cells, as well as inflammatory cells.[7] These substances cause degradation of the corneal collagen and extracellular matrix (ECM), and apoptosis of the keratocytes resulting in tissue loss. The remaining keratocytes are converted to activated fibroblasts which are reflective, and the newly synthesized collagen and ECM, which are laid down irregularly. Both these processes result in corneal haze or scarring.

Conflict of Interest
Sonal S. Tuli declares that there are no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Steroids have a variety of different effects on ulcers, some of which are beneficial and others that are potentially harmful. Steroids, on one hand, inhibit the production of inflammatory cytokines like interleukin-1 (IL-1), IL-6, and IL-8 which cause cell infiltration, corneal melting, and neovascularization.[8,9] They also inhibit neutrophil chemotaxis which reduces the amount of inflammation in the eye which, in turn, reduces the inflammatory cytokines as well as collagenases.[10] However, not all the effects of corticosteroids are beneficial. Dexamethasone was found to decrease the migration of epithelium and epithelial healing in patients after refractive surgery as well as in experimental alkali burns.[11,12] In addition, due to the inhibition of the neutrophils, they inhibit the body's natural defenses against infection and can worsen infections or cause recurrences, especially in pseudomonas related infections of the cornea if inadequately treated with antibiotics.[13,14]

Animal experiments had shown some benefit to using steroids to mitigate the effects of inflammatory mediators in bacterial keratitis.[15,16] However, using steroids in patients with infectious keratitis has been controversial with arguments both for and against steroids in literature.[17,18]

In response to the controversy, there were a number of small studies conducted to evaluate the effect of steroids on infectious ulcers.[19–21] They concluded that there were no beneficial or adverse effects of using steroids in corneal ulcers but that larger studies were needed to adequately assess the effects on visual acuity. In 2006, the Steroids for Corneal Ulcers Trial was initiated to answer these questions.[22,23] The study as well as it's sub-studies, are the best evidence we have at present to answer this controversy.

Steroids for Corneal Ulcers Trial (SCUT)

The SCUT was initiated in 2006, completed enrollment in 2010 and was published in 2012. It was a 1:1 randomized, placebocontrolled, double-masked clinical trial comparing prednisolone phosphate, 1%, with placebo as adjunctive therapy for the treatment of culture proven bacterial corneal ulcers. The patients were all pre-treated with moxifloxacin for 48 hours prior to initiation of study medication. Their primary aim was improvement in vision 3 months after enrollment and secondary aims were rates of corneal perforation, size of the scar and rigid contact lens–corrected visual acuity at 3 weeks, 3 months, and 12 months, time to resolution of the epithelial defect, and BSCVA at 3 weeks and 12 months. An additional aim was to assess the correlation between minimum inhibitory concentration to moxifloxacin and clinical outcomes.

440 patients completed the trial and had similar baseline characteristics except the steroid group had statistically significant more central ulcers encompassing the entire 4-mm pupil (P=0.02). There was no statistically significant difference in the visual acuity, rate of perforation, infiltrate/scar size, or epithelial healing between the groups. Interestingly, the placebo group had a statistically significant increase in intraocular pressure (25–35 mm Hg) compared to the steroid group (P=0.04).

Subgroup analysis:

1. Baseline BSCVA: Patients with BSCVA of counting fingers or worse had a significant improvement in visual acuity by approximately 1.5 lines compared to placebo at 3 months (P=0.03).
2. Central location of ulcer: Ulcers completely covering the central 4-mm pupil had an approximately 2 line improvement in the steroid group compared to the placebo group (P=0.02).

3. Ulcer depth: Deep ulcers had an approximately 1.5 line improvement in visual acuity compared to placebo but this was not significant (P=0.07).
4. Ulcer size: Ulcers in the largest quartile of infiltrate size at baseline had an approximately 1.5 line improvement in the steroid group compared to the control group but this was also not significant (P=0.07)

Pseudomonas and Steroids

Pseudomonas is of particular concern when treating bacterial keratitis due to the fulminant infections it causes. Therefore, the investigators of the SCUT performed a subgroup analysis comparing the pseudomonas ulcers with the other organisms. They also compared the outcomes in the pseudomonas ulcers in the treatment and the control groups.[24] Of the 500 patients in the SCUT, 110 patients had pseudomonas. These were compared to the 384 patients with other bacterial infections (6 were not included in this study as they had mixed bacterial infections) and it was found that patients with pseudomonas ulcers presented with significantly worse visual acuities compared to patients with other bacterial ulcers (P=0.001). However, at three months, the pseudomonas ulcers showed a significantly greater improvement in visual acuity than other bacterial ulcers of similar presentation severity (P=0.004).

When the response to steroids in the pseudomonas group was compared to that of the other bacterial ulcers, there was no difference in response between the two groups.

Comparing the pseudomonas ulcers in the steroid treated group with the placebo group, there was no difference in the response rate or complications between the two groups. Specifically, the rates of perforations, increased IOP, epithelial healing or recurrence of epithelial defect were no different between the two groups.

Cytotoxic vs. Invasive Pseudomonas and Steroids

Invasive strains of pseudomonas encode for *exoS*, which allows them to sequester intracellularly and replicate. Cytotoxic strains, on the other hand, lack *exoS* and code for *exoU* instead, and can rapidly kill cells. Of the total number of patients with confirmed pseudomonas in the SCUT, 56 were invasive and 18 were cytotoxic (the remaining were found to have atypical genotypes).[25] They found that invasive isolates had larger infiltrate/scar sizes at baseline (P=0.049) but better visual acuities when controlled for ulcer location (P=0.008). However, at 3 months, invasive strains were associated with an approximately 3.5-line less improvement than cytotoxic strains (P=0.03). When comparing the effect of steroids, they found that invasive ulcers had a 2.5 line greater improvement in visual acuity with steroids compared to placebo. Further, they found that the percentage invasiveness was associated with a significant difference in the visual acuity improvement between the steroid and placebo arms. On the other hand, cytotoxic ulcers in the steroid arm had a 5.5 line less improvement in vision at 3 months compared to placebo but this did not reach statistical significance.

Nocardia and Steroids

Nocardia was found to be a common cause of infectious keratitis in the SCUT with approximately 11% of the 500 enrolled patients diagnosed with Nocardia as the only causative organism.[26] The majority of these had a history of preceding trauma (58%) and were agricultural workers. The Nocardia patients had a relatively long duration of symptoms prior to presentation compared to the non-Nocardia patients (10 days vs. 4 days), and had relatively better vision (20/45 vs. 20/145, P=0.001). The different Nocardia species were variably sensitive to fluoroquinolones ranging from 45% to 100%. They found that, on

average, the use of corticosteroids was associated with a 0.40 mm larger infiltrate or scar at 3 months (P=0.03).

Steroids and Endophthalmitis

A study from Miami evaluated the risk of developing endophthalmitis following infectious keratitis over a 15 year period at their institution.[6] While they found that the overall risk was low (0.5%), 76% of the ones that progressed to endophthalmitis were on topical steroid therapy in conjunction with antibiotics. They also found that the outcomes of these patients were poor with vision less than 5/200 in two thirds of the patients, and enucleation or evisceration was needed in almost a third of the patients.

Conclusions

Although the SCUT was a very well planned and executed study, it did have some limitations. Over a quarter of the patients evaluated were considered ineligible as they were impending perforation. This eliminated the most severe ulcers from the trial. 97% of the patients enrolled were in India and only 3% of the patients were from the US. Thus, results from the study may not be applicable to the US population. For example, there were only 8 contact lens wearers in the entire group of 500 while there was a history of trauma in more than 300 patients. However, in the western countries, contact lenses are the single most common cause of infectious keratitis with trauma a much more minor cause.[2] The distribution of causative organisms was also statistically different between the US and India with over 50% of Indian infections caused by Streptococcus pneumonia and 11% by Nocardia – neither of these was found in the US patients.[22] In addition, all patients were treated with moxifloxacin and the antibiotic was not modified based on organism or sensitivities although the SCUT did find that the organisms varied greatly in the MIC (minimum inhibitory concentration) and percentage that were sensitive to fluoroquinolones.[27,28] The steroid used was prednisolone phosphate and was given in a standard dosage schedule of 4–2-1 times a day for a week each. It is possible that a more aggressive dose would have had a different outcome.

Regardless of the limitations, the study did demonstrate that although there was no benefit to giving all bacterial keratitis cases topical steroids as an adjunct to antibiotics, there was little harm too. There was no increased incidence of perforation, delayed epithelial healing, or intraocular pressure increase in the steroid group. The SCUT also showed that, in select cases, steroids could be beneficial. Central ulcers, ulcers with a vision of count fingers or worse, and perhaps the larger and deeper ulcers would probably benefit from adjunct steroids. On the other hand, steroids would be definitely contraindicated in Nocardia cases. While invasive species of Pseudomonas also had significant improvement with steroids, typing bacteria to determine invasiveness is probably not practical. However, since the two types of pseudomonas has different effects on the cornea, larger ulcers that are not as dense are likely invasive and would benefit from adjunct steroids. On the other hand, smaller but denser and more necrotic ulcers are more likely cytotoxic and not as likely to respond to steroids. However, caution must be exercised when treating corneal ulcers with steroids as they are absolutely contraindicated in fungal keratitis. Therefore, a definitive diagnosis of bacterial keratitis must be available before steroids are started. Unfortunately, diagnosing bacterial keratitis using clinical features is not reliable and cultures should be used to diagnose bacterial keratitis prior to treatment with steroids.[29]

While we have a lot more information in the last two years about the role of steroids in bacterial keratitis, we still have a lot to learn about the optimal timing, optimal organisms, and optimal dose where steroids would improve the current outcomes of bacterial keratitis.

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