ADVANCED SURGICAL AND MEDICAL PROCEDURES IN THE EQUINE CORNEA

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Introduction
In this lecture, we will discuss the use of intrastromal injections, photodynamic therapy (including cross linking), and minimally invasive surgeries for treatment of equine cornea disorders, such as infectious and immune-mediated keratitis in horses.

Introduction
With advances in ocular therapeutics and techniques, equine corneal disease that traditionally required surgery can increasingly be managed “medically”. Specifically, intrastromal injections of antifungals for treatment of deep stromal abscesses, photodynamic therapy for treatment of immune-mediated keratitis (IMMK), riboflavin photo-crosslinking for melting ulcers, mesenchymal autologous stem-cell therapy for treatment of stromal ulcers and IMMK, and immunomodulatory gene-addition gene therapy for IMMK.

Intrastromal injections
The mainstay of ocular therapeutics, especially treatment of the cornea, is topical eye drops, which have many disadvantages, such as inefficient drug penetration, high systemic drug absorption, the need for frequent re-application due to low surface residence time, and patient self-administration. These disadvantages lead to suboptimal efficacy, possible toxicity, and lack of compliance. The need for better and more efficient ocular drug delivery, especially to the cornea and anterior segment, is sorely needed.

Corneal intrastromal injections are becoming increasingly routine for treatment of infectious keratitis (i.e., fungal and bacterial infections) and corneal neovascularization. The goal of these injections is to increase the local concentration and exposure time of the drug in the deep corneal stromal layers. As alternatives to topical application, several sustained release devices, including dissolving inserts, contact lenses, and gels have demonstrated promise as ocular drug delivery devices, but these approaches do not directly target the corneal stroma and have similar disadvantages as topical application in regards to off-target tissue drug exposure. Corneal intrastromal injections address many of these disadvantages. Currently, intrastromal injections rely on the use of 27-31 gauge needles directed obliquely into the cornea, however, they are technically difficult, result in variable injection locations and depth, vary between the clinician, and require the need for magnification, such as an operating microscope, to perform the injections. Therefore, a precise injection method that allows reproducible corneal stromal drug delivery is needed for targeted corneal therapeutics.

Our laboratory at NC State university has developed and evaluated a purpose designed precise corneal injection (PCI) needle. The PCI needle is a depth-defined injection device that not only provides accurate and safe intrastromal drug delivery, but is intended to be performed on patients without use of magnification and with only local anesthesia. The data demonstrate that PCI needles provides reproducible, uniform, and precise site-specific corneal drug delivery by a simple macroscopic procedure. When coupled with its ease of use, PCI needles reduce consequential
variables, compared to current corneal injection technologies, and are ideal for routine drug applications for corneal disease including gene therapy.

**Current use of intrastromal injection in horses.** Corneal stromal abscesses are most commonly fungal in origin. Therefore, in cases of corneal stromal abscesses in which the horse was not a candidate for general anesthesia, intrastromal (intrallesional) injection of 1% to 5% voriconazole has been used. This method was used to cause a high concentration of drug into the lesion. Either a 30 G needle or purpose-designed microneedle is used for the injection. Volume of injection ranges from 0.2 to 0.5 ml. Horses with substantial stromal loss or uveitis have a poorer outcome. Several studies have demonstrated resolution of the lesions without surgery.

**Other promising therapies**

*Photodynamic therapy*
Intralesional injection with Rose Bengal solution followed by diode laser irradiation has been recently reported as a treatment for equine IMMK (McMullen, IEOC 2016). Early results appear promising.

*Corneal collagen cross-linking*
A method of accelerating healing of corneal ulcers is corneal collagen cross-linking (CXL). CXL is induced by illumination of the corneal stroma with ultraviolet light (UVA) after instillation of riboflavin (vitamin B2) eye drops. This is hypothesized to induce changes in the collagen which stabilizes stromal breakdown, and has been used successfully to treat infectious ulcerative keratitis in horses (melting ulcers).

*Autologous bone marrow-derived mesenchymal stem cells (MSCs)*
Bone marrow derived mesenchymal stem cells (MSCs) are non-hematopoetic, multipotent cells derived from adult bone marrow; characteristics of MSCs include ease of isolation, proliferative potential, and ability to differentiate into various cell types. Application of MSCs, or supernatant derived from MSCs cultures, to injured cornea has been demonstrated to improve corneal wound healing in both rats and rabbits. Ocular benefits of MSCs include increased survival and proliferation of limbal epithelial cells, direct differentiation into epithelial-like cells, and suppression of corneal inflammation, among others. Mesenchymal stem cells can be applied directly to the cornea or administered via intrastromal, subconjunctival, or systemic injections. Bone marrow derived MSCs have been used for many years now to treat musculoskeletal diseases in horses.

Ongoing experimental studies have demonstrated improved and quicker healing of stromal corneal cell defects – additional work is needed to determine indications and therapeutic routes.

Subconjunctival autologous MSCs (1x10⁶) in 0.5ml serum has been used subconjunctivally in horses with IMMK. In an on-going clinical trial, 5 of 6 horses have had complete resolution of IMMK without additional treatment. Further study is needed to determine overall efficacy and duration of effect, but early data looks very promising.
Further reading:
