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A REVIEW ON ADVANCED TREATMENT TECHNIQUES FOR FUNGAL KERATITIS

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ABSTRACT

Fungal keratitis or fungal corneal ulcer is potentially binding infection of cornea, is considered one of the major cause of ocular morbidity, particularly in developing countries. Infectious keratitis is frequently caused by it, particularly in tropical and subtropical nations. Mycotic or fungal keratitis, as well as keratomycosis, are fungus-related infections of the cornea that manifest as purulent, typically ulcerative, lesions. Because of its propensity to mimic other forms of stromal inflammation and because its care is limited by the availability of potent antifungal drugs and their capacity to enter corneal tissue, this type of corneal infection presents a challenge to the ophthalmologist. Fungal keratitis is renowned for being hard to diagnose and treat. Reports of mycotic keratitis have been received from all over the world, but especially from tropical regions where it may be responsible for over half of all cases of microbial keratitis and ocular mycoses. There are two primary kinds that are known to exist: keratitis caused by yeast-like and related fungus (specifically Candida) and those caused by filamentous fungi (mostly Fusarium and Aspergillus), which are widespread in tropical and subtropical zones. Fungal infections in the cornea can have irreversible aftereffects if treatment is postponed. Treatment results for fungal keratitis are frequently worse than those for bacterial keratitis. The main causes of the poor result are inadequate antifungal medications and delayed diagnosis. Significant progress in treatment has been made in the last few years. The pathophysiology, clinical characteristics, therapy, and epidemiology of fungal keratitis are reviewed in this topic.

KEYWORDS: Infectious keratitis, fungal keratitis, Aspergillus, antifungal medications and keratoplasty.

INTRODUCTION

A fungal infection of the cornea, the transparent dome covering the coloured portion of the eye, is known as fungal keratitis. Aspergillus, Candida, and Fusarium species are a few of the fungi that can cause fungal keratitis. Microbial keratitis can arise from bacteria, viruses, fungus, or protozoa. Since it was first reported in 1879, the occurrence of fungal keratitis (FK) has been rising during the previous 30 years. It represents between 40% and 50% of all instances of microbial keratitis.[1] FK is a dangerous illness that, if left untreated, can cause endophthalmitis, destroy corneas, and cause a significant loss of eyesight. Therefore, early detection and treatment are crucial to avoiding long-term consequences, such as blindness.

Fungal keratitis may have been spurred on by more than 100 distinct fungus species. Both yeast and filamentous fungus, which are subclasses of monomorphic fungi, cause Fungal Keratitis instances. Numerous variables, such as individual risk factors, local temperature, climate, geography, and urbanisation, influence the particular type of fungus that causes Fungal Keratitis. The most common personal risk factors linked to FK are trauma, immunocompromised states, ocular surface diseases, and contact lens wear. These circumstances may also make one more susceptible to other fungal infections. Fungal keratitis can be difficult to cure clinically, although recent research techniques including amniotic membrane transplantation, corneal collagen cross-linking, and penetrating keratoplasty[3] can be useful.[2]

Symptoms[3, 4]

- Eye pain
- Eye redness
- Blurred vision
- Sensitivity to light
- Excessive tearing
- Eye discharge

Etiology

Many fungal species can result in FK, however, the most commonly implicated are Fusarium, Aspergillus, and Candida species. The causative organism of FK may differ according to several factors including regional temperature, climate, and urbanization. In a study performed in India on FK, Aspergillus species were the most commonly isolated species followed by Fusarium. This was also confirmed in several other studies from India, with one study showing that Aspergillus was responsible for more than 55% of all FK cases, suggesting that Aspergillus species are the most common cause of FK in the Indian subcontinent. Other studies, however, have shown that Fusarium was the most common aetiology of FK in other parts of the world including south India. In a large study from the USA over a 7year period, 39% of FK cases were caused by Fusarium, while 22% were caused[5,6] by yeasts including Candida. In another study of 2065 cases of confirmed fungal keratitis in central China, the predominant fungal species was also Fusarium (>50%), followed by Aspergillus (>9%) and Alternaria (>7%). Corneal[9] refractive surgery including laser in situ keratomileusis (LASIK) may also rarely be a cause of fungal keratitis that could lead to severe consequences if not properly treated.[7] Various fungal species responsible for post-LASIK FK have been isolated including *Candida*, *Fusarium*, *Aspergillus*, and *Alternaria* species. This could be due to inappropriate operative room sterilization techniques or poor postoperative hygiene.

Epidemiology[10, 15]

Like most infectious diseases, geographical location, and socioeconomic status influence the prevalence and cause of FK. In the United States, warm places in southern locations like Florida have a higher incidence of FK compared to colder places in the north. *Fusarium*, *Candida,* and *Aspergillu*s are the most frequently isolated species causing FK in the USA, while in India, *Aspergillus* is the most common cause. *Fusarium* is a particularly common cause of FK in warm climates such as Brazil,] while *Candida* may be more common in temperate climates. The overall incidence of FK seems to be markedly higher in certain parts of the world. In a study of FK in Hyderabad India, 1360 patients with FK were seen over a period of 10 years in a single institute, while in a study from central China, 2065 cases were documented over a 9year period. In a study in Melbourne Australia, however, only 56 cases were seen in 8 years, while in a study from New York, only 61 eyes with FK were documented over a 16year period. This may be due to climate, environmental, occupational, or behavioral differences.

Several studies have shown a higher incidence of FK in young adult males, possibly due to more outdoor activities and a higher incidence of trauma. In a large study of Chinese patients with FK, more than 60% were males, and more than 75% were aged between 30 and 60 years.

CONVENTIONAL TECHNIQUES[12]

The conventional techniques which are used to treat ocular drug delivery systems are

- Suspension
- Emulsion
- Ointment
- Solution
- Insert
- Gels

Advantages

- Ease of bulk scale manufacturing
- High patient acceptability
- Drug product efficacy
- Stability and cost-effectiveness

Disadvantages

- Poor bioavailability
- Frequent dosing

NOVEL TECHNIQUES[13]

The novel techniques are efficient for the treatment of fungal keratitis.

OBJECTIVES

- To increase accurate dosing.
- To overcome the side effects produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of the drug by increasing the cornel contact time.
- To overcome the protection barriers like drainage, lacrimation, and conjunctival absorption.
- To provide comfort, better compliance to the patient, and to improve therapeutic performance of the drug.

The novel techniques which are used for the treatment of fungal keratitis are[14]

- Penetrating Keratoplasty
- Lamellar Keratoplasty
- Rose Bengal Photodynamic Therapy
- Amniotic Membrane Transplantation
- Corneal Collagen Cross Linking
- Hydrogel-Based Hybrid Theranostic Contact Lens
- Low-temperature plasma Radiofrequency Ablation surgery

PENETRATING KERATOPLASTY

Penetrating keratoplasty (PKP) or optical penetrating keratoplasty (OPK) is a technique of performing full-thickness corneal transplantation where a diseased cornea is removed and replaced with a healthy and viable donor corneal button. Eduard Konrad Zirm was the first to perform a solid organ corneal transplant in 1905. He successfully completed the first full-thickness corneal transplant. The surgery was performed on a patient with bilateral alkali burns. Vladimir Petrovich Filatov, a Russian ophthalmologist, is known as the father of keratoplasty as he was the one who suggested that cadaveric cornea can be used as a donor cornea for performing keratoplasty.

Types of Penetrating Ketatoplasty

- **Tectonic:** To restore the anatomical integrity of the globe
- **Therapeutic/ reconstructive:** To eliminate the infective load from the eye
- **Cosmetic:** Keratoplasty is done to remove the corneal opacity
- **Optical:** Keratoplasty is done to restore vision.

Surgical Procedure

Before initiating the surgery, the surgeon should decide on the appropriate size of the corneal trephine and donor punch. Typically, a trephine is selected to encompass the entirety of the corneal pathology (e.g. in cases of microbial infections). Sometimes in the case of microbial keratitis, the infection extends beyond the limbus. In these cases, the surgeon may choose to perform a larger corneoscleral graft. In other extensive cases, such as with corneal dystrophies, corneal trephination may not include the entirety of the pathology. In these cases, a smaller graft can be used as long as it allows for the visual axis to be clear. The use a corneal button 0.25-0.50mm larger than the diameter of the host corneal opening is recommended as it can help reduce excessive postoperative corneal flattening, reduce the risk of secondary glaucoma, and enhance wound closure.

Treatment

Start a topical steroid, such as prednisolone acetate 1%, every 1 to 2 hours immediately. Use a cycloplegic agent. Systemic steroids (prednisone 40-80 mg daily) should be considered in cases that do not respond to topical steroids and in recurrent rejection episodes.

LAMELLAR KERATOPLASTY

Lamellar keratoplasty is an operation in which diseased corneal tissue is removed and replaced by lamellar corneal tissue from a donor. The procedure is performed either to improve vision (optical keratoplasty) or to provide structural support for the cornea (tectonic keratoplasty). Lamellar keratoplasty can be performed to replace just a portion of the corneal thickness when the endothelium is healthy. Depending on the location of the corneal abnormality, it may be sufficient to replace just the anterior layers with lamellar keratoplasty, or the full thickness of the corneal stroma without endothelium, with deep lamellar keratoplasty. Postoperative care involving the use of appropriate immunosuppressive therapy often influences the results of optic keratoplasty as well as tectonic keratoplasty.

ROSE BENGAL PHOTODYNAMIC THERAPY

St. Louis, MO, USA) were diluted for one minute in 5mL of balanced salt solution (BSS) (Alcon Laboratories, Fort Worth, TX, USA), while shaking the container to achieve a Rose Bengal solution Four or eight strips of Rose Bengal (RB) (Glostrips 1.3mg, Amcon, concentration of 0.1% or 0.2%, respectively. Concentration of Rose Bengal solution was selected by the clinician based on the severity, clinical response to prior treatments and/or in vitro data regarding the susceptibility of the microorganisms to Rose Bengal PDAT.

AMNIOTIC MEMBRANE TRANSPLANTATION

Amniotic membranes are tissue rich in stem cells that function as a short- term corneal graft. It is applied in-office by an eye doctor, and is a quick and simple procedure. The membrane is secured in a flexible round ring, which is inserted underneath the upper and lower eyelids so that the membrane is completely covering the front of the eye. The eyelids are usually secured shut for several days with surgical tape or gauze to keep the membrane safeguarded. Over the matter of a few days, the amniotic membrane is slowly absorbed by the corneal tissue, and the regenerative stem cells begin to repair the damage ocular surface. The membrane is completely absorbed or dissolved within 7-10 days, and the plastic ring is removed from its position beneath the eyelids. This is how the technique of amniotic membrane transplantation is performed.

CORNEAL COLLAGEN CROSS-LINKING

Corneal collagen cross-linking (CXL) has been found successful in halting the progression of keratoconus by using riboflavin and UV-A light.

Riboflavin

- A photosensitizer is a molecule that absorbs light energy and produces a chemical change in another molecule.
- In CXL, Riboflavin is used as the photosensitizer. It is safe systemically and can be adequately absorbed by the corneal stroma typically. It has an absorption peak of 370nm.

UV Light

- As the absorption peak of riboflavin was noted to be at 370nm, UV-A light was found to be ideal for CXL, while at the same time protecting the other ocular sutures. The total fluence was found to be 5.4J/cm2.
- The Bunsen Roscoe law states that photochemical effect should be similar if the total fluence remains constant. Based on this, various protocols have been

devises with different combinations of the intensity and duration of UV-A exposure. However, it has been noted that CXL fails to be effective once the energy intensity exceeds 45Mw/cm^2.

HYDROGEL-BASED HYBRID THERANOSTIC CONTACT LENS

Fungal keratitis, a severe ocular disease, is one of the leading causes of ocular morbidity and blindness, yet it is often neglected, especially in developing countries. The therapeutic efficacy of traditional treatments such as eye drops is very limited due to poor bioavailability, whereas intraocular injection might cause serious side effects. Herein, we designed and fabricated a hybrid hydrogel-based contact lens that comprises quaternized chitosan (HTCC), silver nanoparticles, and graphene oxide (GO) with a combination of antibacterial and antifungal functions.

The results from in vitro and in vivo experiments demonstrate that contact lenses loaded with Voriconazole have excellent efficacy in antifungal activity in vitro and could significantly enhance the therapeutic effects on a fungus- infected mouse model. The results indicate that this hydrogel contact lenses-based drug delivery system might be a promising therapeutic approach for a rapid and effective treatment of fungal keratitis.

LOW-TEMPERATURE PLASMA RADIOFREQUENCY ABLATION SURGERY

Fungal keratitis is a type of blindness-causing keratopathy caused by pathogenic fungal infection and ranks first in the rate of blindness due to infectious keratitis. A fungal corneal ulcer increases the chance of transplant rejection since anti-hormone rejection drugs cannot be used following keratoplasty. Therefore, it is critical to research and develop effective and safe treatments for fungal keratitis (FK), to slow down the adverse impact on the vision of patients with FK.

CONCLUSION

Fungal keratitis treatment is still an ongoing challenge for corneal experts. The low prognosis for fungal keratitis has been further compounded by newly emerging fungal infections and resistance to currently available antifungal medications. Fungal keratitis can be treated using more advanced investigational techniques as Rose Bengal Photodynamic Therapy, Corneal Collagen Cross-linking, Amniotic Membrane Transplantation, Penetrating Keratoplasty, and Lamellar Keratoplasty.

REFERENCES

1. A.V. Sitnova, S.N.Svetozarskiy. Modern Technologies in Diagnosis of fungal keratitis sovrem Technologii Med, 2023; 15(2): 73-84.
2. Ahmed Abdel-Hadi, Yendrembam Randhir Babu Singh, Rajaman Revathi et.al. Fungal Keratitis: Epidemiology, Rapid Detection, Antifungal susceptibilities of fusarium and Aspergillus Isolates from corneal scrapings. Biomed Res Int, 2019; 19(3): 246-267.
3. Alan N. Carlson, Landan Espandar. Lamellar Keratoplasty: A Literature Review. J Ophthalmol, 2013; 14(9): 396-401.
4. Bi Bhudutta Rautaraya, Savitri Sharma, Srikant K sahu. Diagnosis and treatment outcome of mycotic Keratitis at a tertiary eye care center in easter india. BMC Ophthalmology, 2011; 10(9): 610-635.
5. Dideeya Ali, Ann Tresa Antony, Ajith Vijayan et.al. Challenges in the diagnosis and management of typical fungal keratitis during the COVID-19 Pandemic: a case series. MicroSoc, 2023; 5(8): 268-287.
6. Donald Stone, Jeremy F.Tan. Fungal keratitis: Update for 2014. Curr Ophthalmol Rep, 2014; 16(2): 129-136.
7. Jack S. Parker, Korine Van Dijk, Gerrit R.J.Melles et.al. Treatment options for advanced keratoconus: A review. Surr Ophthalmol, 2015; 60(5): 459-480.
8. Jian-Fei Huang, Jing Zhong, Guo-pu Chen et.al. A Hydrogel-Based Hybrid Theranostic Contact Lens for Fungal Keratitis. ACS Nano, 2016; 10(7): 6464-6473.
9. L Hazlett, Susmit susvas, Sharon McClellan et.al. Challenges of Corneal infection. Expert Rev Ophthalmol, 2016; 11(4): 285-297.
10. Lottie Brown, Astrid K Leck, Michael Gichangi et.al. The global incidence and diagnosis of fungal keratitis. Lancet Infect Dis, 2021; 21(3): 340-367.
11. Mikk Pauklin Henning Thamasen, Daniel Meller et.al. Amniotic Membrane Transplantation in the Human Eye. Dtsch Arztebl Int, 2011; 108(14): 243-248.
12. Namrata Sharma, Bhupesh Baggaetal. Fungal Keratitis: A review of clinical presentations treatment strategies and outcomes. Ocul Surf, 2021; 24(3): 324-365.
13. Namrata Sharma, Ritu Nagpal, Vishal Jhanji et.al. Recent Advances in diagnosis and management of Mycotic Keratitis. Indian J Ophthalmol, 2016; 64(5): 346-357.
14. Nimmy Raj, Murugesan Vanathi, Nishat Hussain Ahmed et.al. Recent Perspectives in the Management of Fungal Keratitis. J Fungi (Basel), 2021; 7(11): 907.
15. P.A. Thomas, J. Kaliamurthy.Mycotic Keratitis: epidemiology, diagnosis, and management. CMI, 2013; 19(3): 210-220.