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Review Article

A Comparison Between Intrastromal Voriconazole and Intracameral Amphotericin B in the Treatment of Resistant Fungal Keratitis

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ABSTRACT

Background: According to reports, fungus-related keratitis accounts for roughly 50% of all bacterial keratitis instances involving therapeutic penetration keratoplasty, making it a significant contributor to ocular morbidity. Fungal keratitis is a difficult condition to identify and manage.
Patients and Methods: A prospective investigation was carried out. A total of 40 eyes from 40 participants with fungal keratitis (26 men and 14 women) were enrolled in this study. Grouping 20 eyes first go through Voriconazole intrastromal Grouping 20 eyes are examined again with Amphotericin B injection.
Results: Following intrastromal voriconazole administration, the satellite lesions in 9 participants and the hypopyons in 3 individuals in the first cohort vanished without subsequent infection or ocular rupture. After injections, the infiltration's size considerably shrank to 5.41± 2.21 mm (P <0.001), but the ulcer's size remained the same (4.25 ±1.83 mm, P = 0.071). Seven of the 17 effectively hospitalized groups in the first patient received just one injection, while six received two injections, and four received three.
Conclusion: The treatment of fungal keratitis is still difficult. The causes for the poor prognosis in fungal keratitis are compounded by newly emerging fungal infections and resistance to already available antifungal medications. For persistent deeply fungal corneal ulcers, intrastromal voriconazoles and intracameral amphotericin B seem to be a successful therapy option. Thus, we draw the conclusion that in some individuals, intrastromal voriconazole may be administered as a replacement for fungal ulcers that do not heal.

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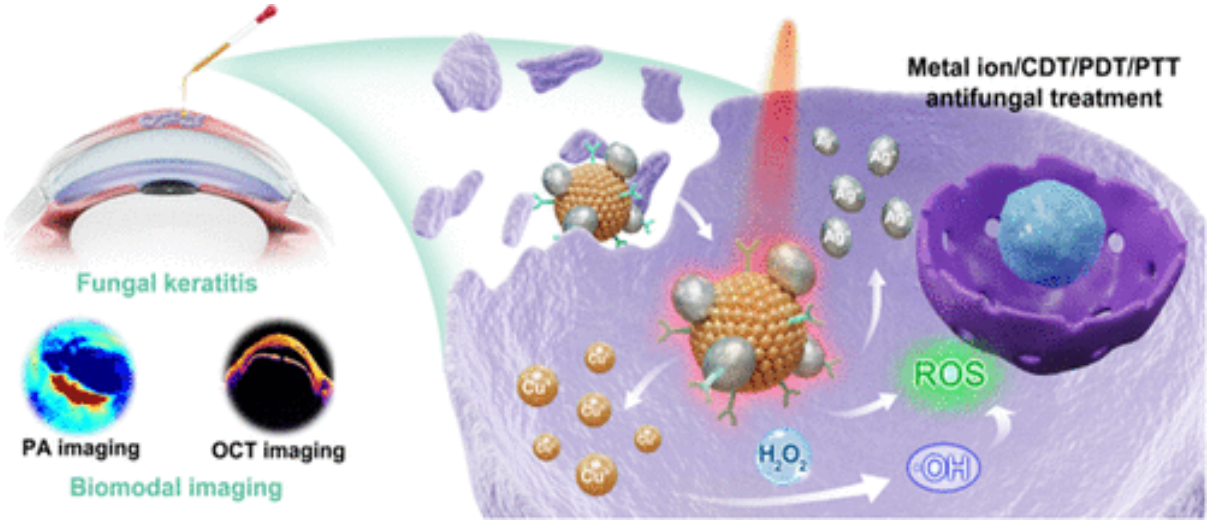
GRAPHICAL ABSTRACT



Introduction

According to reports, fungus-related keratitis accounts for roughly 50% of all bacterial keratitis instances involving therapeutic penetration keratoplasty, making it a significant contributor to ocular morbidity. Fungal keratitis is a difficult condition to identify and manage. In addition, it is frequently misdiagnosed as another infectious keratitis since its beginning phase typically lacks adequate clinical and microbiological evidence, delaying treatment [1].

When opposed to bacterial keratitis, fungal keratitis has been observed to have inferior therapeutic efficacy. Furthermore, there are not many commercialized topical antifungal medications, and most of them have limited corneal penetrations [2].

Ocular trauma, ocular surface illness, lens care usage, topical steroid use, and systemic immunosuppression are risk factors for fungus keratitis. Of these, it has been demonstrated that earlier use of topical corticosteroids is a therapeutically significant factor since it may worsen the infections, It is challenging to assess clinical progression when topical steroids are used in the initial phases of viral keratitis because they temporarily increase the immune-inflammatory responses in the corneal stroma while decreasing the host's immunological responses [3].

The keratitis caused by fungi is more dangerous and aggressive [1]. The related risk elements of fungal keratitis include lens care utilization, topical steroid use, and eye trauma from vegetative issues. Males are more likely than females to experience it [4].

Structure-activity relationship (SAR) indicated interesting *in vitro* antimycobacterial activity patterns against M. tuberculosis H37Rv (MTB) [5].

At least 70 genera and numerous species of fungus have been discovered as the causative agents of fungus keratitis, with tropical strains of filamentous fungi like Aspergillus sp. or Fusarium sp. responsible for 70% of cases. Furthermore, various fungi identified from fungal keratitis differ with the examined geographical areas [6]. The cell membrane of fungi consists of ergosterol [7].

There are numerous risk factors associated with fungal keratitis. Yeast strains are often assumed to be linked to systemic immunosuppressive, but filamentous fungi are frequently linked to those who work in agriculture. In a previous retrospective analysis, we discovered that a high ulcer diameter and Aspergillus infections were indicators of a poor prognosis in individuals with fungal keratitis managed with Natamycin 5 percent monotherapy [8].

It seemed obvious that greater ulcers would result in worse outcomes, but the second observation was intriguing. Fusarium was once thought to be a particularly virulent organism. In addition, Jones found that Fusarium solani was much more harmful than Aspergillus in his classic work on the fundamentals of the treatment of otomycosis [9].

According to the results of the MUTT I, NTM is the preferred treatment for filamentous keratitis, particularly those caused by Fusarium species. The most recent developments in treating fungal keratitis medically are described in the next section [10]. Compared with the reference medicine, nystatin has a zone of inhibition of 19.1 mm and exhibits less antifungal potential [11].

A fluoropyrimidines grouping is present in place of the triazoles moiety in VCZ, a triazoles antifungal drug that shares structural similarities with fluconazole. It works similarly to other triazole drugs by blocking the enzymes 14-alpha-lanosterols demethylases, which causes ergosterols levels to drop. Ergosterol is a crucial part of the fungus's cell wall. Compared to mammalian enzymatic reactions, this suppression is far more selective for fungus enzymatic reactions. Candida, Fusarium, and Aspergillus types are only a few of the fungus species that the range of sanctions that VCZ can take against [12]. The VCZ delivery can be done orally, topically, intracamerally, or intrastromally. Both topical and systemic VCZ are effective, according to numerous types of research. Using specialized medicine administration of VCZ, the treatment of fungal keratitis that does not respond to traditional topical therapy has been investigated. Such a method of drug delivery addresses a fundamental problem of topical antifungal medications, restricted drug absorption in cases of severe fungal corneal ulceration. It administers depots of medication close to the inflamed area in 5 sequential doses at a dose of 50 g/0.1 ml, from which the medication is gradually absorbed into the damaged tissues [13]. In several nations, AMB is the first line of therapy for keratitis brought on by Candida species, and in areas where NTM is unavailable; it is employed to treat fungal keratitis. Although less efficient against Fusarium species, AMB is also potent against Aspergillus species. Another method being used for precise medication administration is intracameral AMB. When both local and systemic antifungal therapies have ended in failure, particularly in situations of severe mycosis, endothelial plaques, the existence of hypopyons, and/or anterior chamber dysfunction [14].

Keratoconus development has been reported to be successfully halted by corneal CXL. The CXL involvement in viral keratitis has garnered a lot of attention in recent years. On the effectiveness of CXL in infectious diseases, numerous types of research have been reported with inconsistent findings. At the ninth cross-linking conference in Dublin, Ireland, in 2013, the name "photoactivated chromophores for infectious keratitis (PACK)-CXL" was coined to differentiate the application from CXL for the keratoconus treatment to CXL for viral keratitis [15].

PDT has been employed to treat various conditions including Acanthamoeba keratitis, tumors, choroidal neovascularization in age-related retinitis pigmentosa, and temporal epithelial growth [16]. It gives a visual strategy to understand the relative polarity of a molecule and serves as a useful quantity to explain the hydrogen bonding, reactivity, and structure-activity relationship of molecules [17].

PDT entails the use of various light wavelengths to activate photosensitizers. The lights excite the photosensitizers, which then combine with oxygen-producing ROS and several intracellular ingredients to kill cells. Furthermore, Arboleda *et al.* showed that RB PDT is effective in treating infectious keratitis in an experimental investigation. Yet no therapeutic studies have been done to date to support PDT with RB for the treatments of fungal keratitis [18]. The removal of necrotic tissues containing immune cytokines, pathogens, and toxic debris-products that may further harm corneal tissue-has been employed in relatively superficial lesions to limit infections by enhancing the penetrations of topical medication [19]. The interesting antifungal activity was seen in some compounds, both strongly and moderately [20].

Material and Methods

A prospective investigation was carried out. A total of 40 eyes from 40 participants with fungal keratitis (26 men and 14 women) were enrolled in this study. Grouping 20 eyes first go through Voriconazole intrastromal Grouping 20 eyes are examined again with Amphotericin B injection.

The association of fungal keratitis was founded upon the positively findings of fungal cultures, and individuals with bacteriologically verified fungal keratitis who did not react to topical natamycin (5%) and topical voriconazole (1%) after 2 weeks of therapy were comprised in the research. All participants signed a consent form after receiving full information; the research included all individuals with fungus keratitis involving the midstroma, who were not responding to topical antifungal drugs such as natamycin and voriconazole. Patients having simultaneous endophthalmitis, neighboring sclera involvements, franks, or imminent corneal perforations were eliminated from the research. Slit lamp biomicroscopy was used to investigate the size, locations, and consequences like endothelial plaques, hypopyons, and satellite lesions. Prior to therapy, upon epithelial healing, and at the final follow-up, Best Corrected Visual Acuity (BCVA) was evaluated and documented.

Every participant in group 1 received intrastromal voriconazoles, which was formulated as follows: 50 ug/0.1 mL. Using 20 mL of lactated Ringer's solutions (LR) and 200 mg of voriconazole powders (VFEN, Pfizer, USA), a transparent concentrate containing 10 mg/mL of voriconazole was created. These solutions were then reduced to a concentration of 0.5 mg/mL (50 ug/0.1 mL) in a 1 mL aliquot with 19 mL of LR for injections. Every time, fresh voriconazole injections were made.

Using topical anesthesia (0.4% oxybuprocaine hydrochlorides eye drops), all intrastromal injections were carried out using an operating microscope under aseptic settings. 30-gauge needles were used to put the reconstitute voriconazole (50 ug/0.1 mL) into 1 mL tuberculin syringes. The needle was placed obliquely into the unaffected, clear portion of the stromal with the bevel down to reach the infiltration at the mid-stromal levels.

To create a pharmaceutical deposition all the way around the lesions, voriconazole (0.05 mL) was injected in four evenly-spaced doses. Circumferential injections made sure intrastromal voriconazole barrages formed around the whole infiltration.

Following intrastromal injections, the participants' prior medical treatments with antifungals were resumed. Participants undergo 0.25% amphotericin B or 5% natamycin together with 0.5% fluconazole every two hours or every half hour. In addition, the participants undergo a daily dose of 200 mg of oral itraconazole for 21 days. Patients were evaluated every day, and the slit light was used to track how well the treatment was working. Whenever the corneal infiltration and epithelial defects had fully healed, the disease was deemed to be under control. After the infections had fully resolved, topical antifungal medication was kept for at least two weeks. Participants were seen for keratoplasty with imminent perforations and increasing infiltrates.

All of the patients in the second category get injections of Amphotericin B which was originally purchased as pure powdered and dissolved in 5% dextrose to produce doses of 50 g/mL. Following the administration of peribulbar and topical anesthetic in an aseptic environment, the entire injection operation was performed utilizing an operating microscope.

For the intracameral injections, the endothelium plaques regions, hypopyons, and fungal masses were softly drained and then inoculated on SGA. Limbal incisions were created at the clear corneal edges. Using a 30-gauges needle on a tuberculin syringe, an intracameral injection of 0.5 g amphotericin B (50 μg/mL) was administered.

Depending on the clinical outcome, selectively recurrent intrastromal or intracameral injections were carried out as needed. Recurrent intrastromal treatments were planned with an interval of more than five days when there was a corneal ulcer, opacity, or edema that was getting worse. Periodic intracameral injections were also planned until the fungal masses, hypopyons, and

endothelium plaques in the anterior chambers vanished or till it was determined that the therapy had failed. Repeated intracameral injections were spaced apart by more than three days. In addition to the injections, topical natamycin, fluconazole, and atropines were repeated.

Follow up

All participants experienced everyday evaluations for 10 days, and then every four days until two months, during which time visual acuity, intraocular pressures, complications, and the presence of ocular infections were all assessed. The resolutions of the corneal infiltrates, the absence of the anterior chamber's inflammations, and the repair of the epithelial defects were considered signs of successful treatments.

Inclusion criteria

1) After receiving antifungal treatment for one-week, severe fungal keratitis was not treated, 2) damaged cornea partially, 3) internalization of the eye, 4) widespread opacity and edema, 5) localized descemetoceles with staphylomas, 6) penetrating the membranes of Descemet, 7) endothelium plaques expansion, 8) apparent fungus in the pupillary spaces and anterior chambers.

Exclusion criteria

1) Instances where there was adjacent sclera, 2) transparent corneal perforations, 3) anterior chambers are small, and 4) intravitreal fungus detected by B-ultrasounds imaging.

Safety criteria

We kept an eye out for any adverse reactions linked to intrastromal voriconazole or intracameral amphotericin B, including serious eye discomfort. Also, examinations included any adverse effects from surgery, such as endophthalmitis and corneal ulcers.

Ethical approval

We obtained informed written consent from all participants before getting them involved in the study and discussed with them about steps, aims, potential benefits, and hazards of the work. The study protocol was approved by the Al-Azhar University Local Ethics Committee, Faculty of Medicine (for Boys); all procedures were in accordance with the Declaration of Helsinki.

Table 1: Difference between both groups regarding age and gender

	Group 1	Group 2
No of eyes	20 eyes	20 eyes
Age (mean ± SD)	37.83 ± 21.79 years	39.83 ± 21.65 years
Gender		
Male	13 (65%)	15 (75%)
Female	7 (35%)	5 (25%)

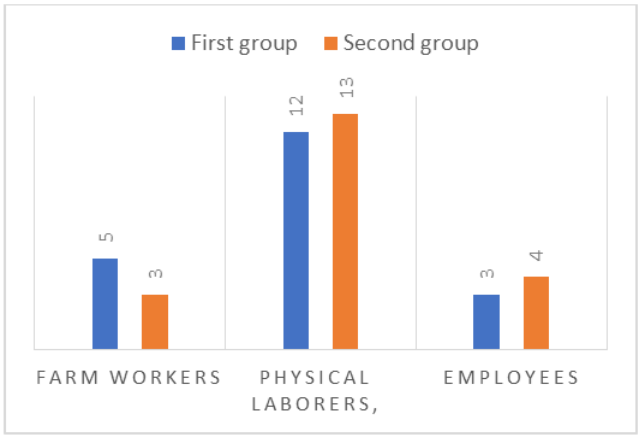


Figure 1: Causes of fungal keratitis in both groups

Results and Discussion

Twenty individuals in the first group were treated with intrastromal voriconazole (13 males, 7 females), the participants' ages ranged from 31 to 75 years, with a mean age of 37.83 ± 21.79 years.

Twenty participants in the second group received intracameral amphotericin B treatment (15 males, 5 females). The age range of the participants was 35 to 65, with an average age of 39.83 ± 21.65 years (Table 1).

In the first group, 3 workers, 12 physically labor, and 5 farm laborers were the participants. The median time from the beginning of indicators to admission was 40.31 days, with a variety of 5 to 12 days. The mean time from the beginning of symptoms to presentations ranged from 7 to 19 days (means, 40.13 ± 9.74 days) in the second group, which included three individuals who worked on farms, 13 individuals who performed manual labor, and 4 individuals who were employed (Figure 1).

Corneal trauma (15 eyes), contact lenses care (3 eyes), and unidentified causes (2 eyes) were the possible causes found in the first category. In the secondly group, they were unknown variables. The risk factors found were contacting lenses usage (4 eyes), corneal trauma (14 eyes), and unidentified causes (2 eyes). Four participants in group 2 had previously undergone topical steroid treatment, while 3 participants in group 1 had a history of diabetes mellitus (Figure 2). Different species of fungal keratitis in both groups are Fusarium, Aspergillus, Curvularia, and A. flavus (Table 2).

Voriconazole administration, the satellite lesions in 9 participants and the hypopyons in 3 individuals in the first cohort vanished without subsequent infection or ocular rupture.

After injections, the infiltration's size considerably shrank to 5.41± 2.21 mm (P <0.001), but the ulcer's size remained the same (4.25 ±1.83 mm, P = 0.071).

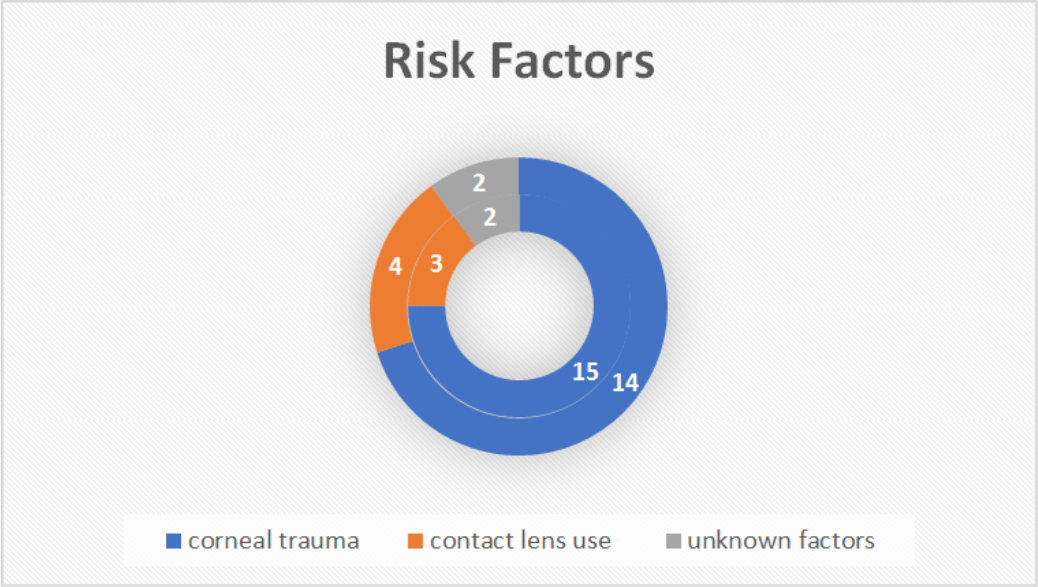


Figure 2: Risk factors in both groups

Table 2: Different species of fungal keratitis in both groups

Fungal species	First group Total number (*n*=20)	Second group Total number (*n*=20)
Fusarium	10 (50%)	9 (45%)
Aspergillus	4 (20%)	6 (30%)
Curvularia	3 (15%)	3 (15%)
A. flavus	3 (15%)	2 (10%)

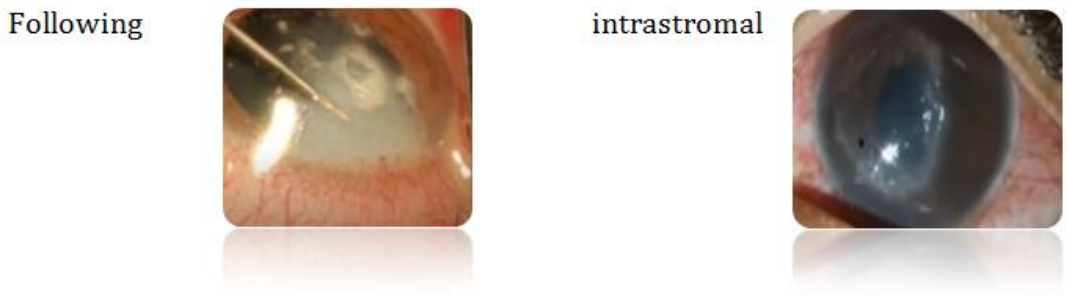


Figure 3: First injection of Intrastromal voriconazole and after 3 injections

Figure 4: The first injection of intracameral amphotericin B and after 3 injections

Seven of the 17 effectively hospitalized groups in the first patient received just one injection, while six received two injections, and four received three. Patient failure number three received four doses. In 17 participants that were healed, the average number of doses was 2.57 1.63. Following treatments, neovascularization occurred in 3 individuals with peripheral lesions and 3 participants with paracentral lesions. Three individuals who eventually had therapeutic lamellar keratoplasty had unsuccessful treatments (LKP). Fusarium was the detected organisms, and it exhibited intrastromal voriconazoles resistance. There were three individuals with peripheral lesions, eight individuals with paracentral lesions, and six individuals with central lesions (Figure 3).

Within group two, five eyes required two injections, five eyes required three injections, and four eyes repaired with just one intracameral injections. The inflammation reaction was seen to wane in the four eyes which only needed one therapy following two days, and the hypopyon vanished between three and ten days after injections (mean, 5.21 ± 3.18 days). Following the initial injection, six eyes with an infection caused by Aspergillus spp. evolved in response, although the cornea exhibited no visible improvements, and on day 5, hypopyon and fungus mass exhibited minor rises. The patients thus had two intracameral injections on days Seven and 12, and the infections had been under control seven days following the initial treatment. 2 individuals who eventually had therapeutic lamellar keratoplasty (LKP) had unsuccessful treatments (Figure 4)

Within the first grouping, the presenter's visual acuity was 6/24 in three eyes (n = 3/20; 15%), 6/36 in twelve eyes (n = 12/20; 60%), 6/60 in three eyes (n = 3/20; 15%), and less than 6/60 in two eyes (n = 2/20; 10%). In the second category, the exhibiting visual acuity was 6/24 in four eyes (n = 4/20; 20%), 6/36 in eleven eyes (n = 11/20; 55%), 6/60 in four eyes (n = 4/20; 20%), and less than 6/60 in one eye (n = 1/20; 5%) (Table 3 and Figure 5).

The clinical signs of fungus invasions, such as corneal infiltrations, hypopyon, endothelium plaques, and fungus masses in the anterior chambers, disappeared in all forty eyes following the therapy. Leucoma treated 7 corneal ulcers in the first sample, and adherent leucoma treated two. Likewise, in the second sample, three people who had persistent leucoma and eight people with leucoma both recovered completely from their infections 18 to 53 days after the initial injections.

Table 3: Visual acuity in both groups

Visual acuity	The first group Total number (*n*=20)	The second group Total number (*n*=20)
6/24	3 (15%)	4 (20%)
6/36	12 (60%)	11 (55%)
6/60	3 (15%)	4 (20%)
< 6/60	2 (10%)	1 (5%)

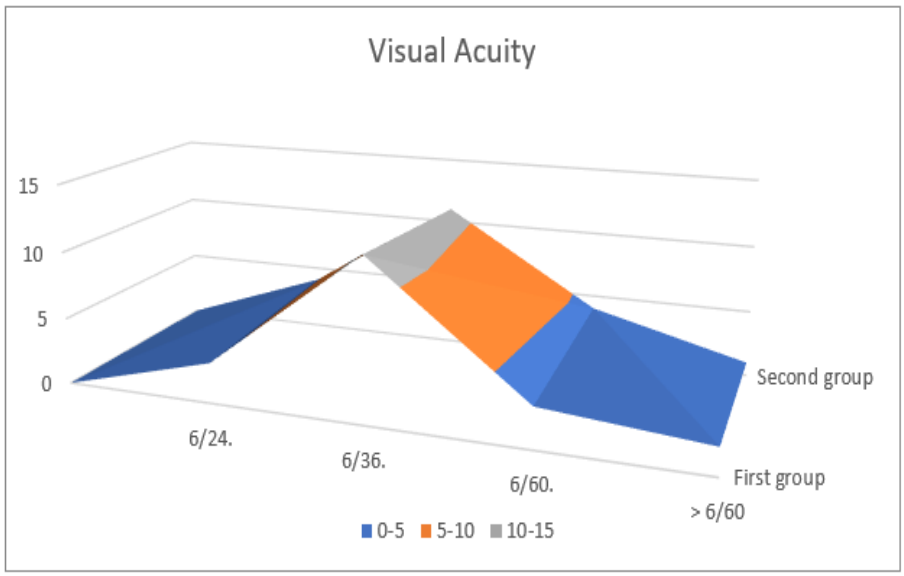


Figure 5: Visual acuity in both groups

Table 4: Clinical data of patients with severe fungal keratitis treated with combined intrastromal and intracameral amphotericin B

	Age (years)/gender	Risk factor for fungal keratitis		Duration of onset of symptoms (days)	Fungal identification		Repeated injection		Healed with	
The first group	37.83 ± 21.79 years	Corneal trauma	15	5-12 days	Fusarium	10	1 injection	7	Leucoma	7
		Contact lens	3		Aspergillus	4	2 injection	6	Ad Leucoma	2
		unknown	2		*Curvularia*	3	3 injection	4		
					A. flavus	3				
The second group	39.83 ± 21.65 years	Corneal trauma	14	7-19 days	Fusarium	9	1 injection	4	Leucoma	8
		Contact lens	4		Aspergillus	6	2 injection	5	Ad Leucoma	3
		unknown	2		*Curvularia*	3	3 injection	9		
					A. flavus	2				

Table 5: Complication in both groups

Adverse Event	Intrastromal Voriconazole (*N* = 20)	Intracameral amphotericin B (*N* = 20)
Secondary Glaucoma	14 (70%)	16 (80%)
Hypopyon	2(10%)	3 (15%)
Uveitis	12(60%)	14(70%)
Progressive corneal thinning	3 (15%)	4(20%)

There was neither vitreous opacity nor band development in either category, and there was also no sign of any systemic or local negative side effects. After discontinuing the use of all antifungal medications, there were no recurrences of the infections (Table 4). The average recovery time was (21.29 ± 6.29) days, and the average follow-up duration was (29.23 ± 6.41) days. Following healings, the corneal depth was (385.29 ± 59.49) mm (414 µM~ 499 µM). The BCVA at the last follow-up was greater than the BCVA after healing (P = 0.019), and the BCVA after healing exhibited substantial improvements when compared to pretreatments (P = 0.01). In the first category, seventeen individuals (n = 17/20; 85%) had VA measurements during the most recent check-in. Four of them (n = 4/20; 20%) saw a modest improvement or no changes in their visual acuity, whereas three (n = 3/20; 15%) saw a decline. In the second category, 18 participants (n = 18/20; 90%) had visual acuity measurements at the most recent follow-up. No statistically significant difference was found. The distinction (P = 0.00) between the two categories of the participants' visual acuity increased or remained the same in 3 (n = 3/20; 15%) individuals and declined in 2 (n = 2/20; 10%) participants.

Complications

Two instances in the inferior's region of the cornea in the first cohort had little intrastromally hemorrhage, but this cleared in 5-7 days. Four participants in each participant received marked increases in pain following intrastromal injections, and all individuals in both groups complained of mild pain right away after the injection. Both the first cohort's 12 patients and the subsequent cohort's 14 cases experienced uveitis. In the first grouping, secondary cohort glaucoma affected fourteen eyes, while in the second category, it affected sixteen eyes. Mannitol was infused intravenously, and Timolol Maleate drops were applied each day to reduce intraocular pressure (Table 5).

Forty eyeballs were divided as participating in our investigation. Twenty eyes in the first group receive intrastromal voriconazoles, whereas 20 patients in the second group receive intracameral amphotericin B treatment. Antifungal drugs, such as topical natamycin, amphotericin B, or fluconazole, either isolated or in combination with oral antifungals, are still the mainstay of treatments for fungal keratitis. Initial results suggest that this strategy is successful. Across both categories, 47.5% of the patients in our research were caused by the fungus Fusarium, which concurs with the findings of Kumar *et al.* research, which found that Fusarium is the most prevalent fungus that causes keratitis [21]. In the first cohort of our research, five individuals worked on farms, 12 patients did manual labor, and three individuals were employed.

The median time from the beginning of symptoms to presentations was 40.31 days, with a range of 5 to 12 days. The average time from the beginning of symptoms to presentations varied from 7 to 19 days (average, 40.13 ± 9.74 days) in the second category, which included 3 participants who worked on farms, 13 participants who performed manual labor, and 4 individuals who were employed. In our research acute perforations, extensive corneal melting, and sudden loss of vision are all symptoms of serious corneal diseases. In contrast to Dursun *et al.* findings' which revealed endophthalmitis, the hypha also penetrated the intact Descemet's membranes and quickly invaded the anterior chambers in this investigation [22].

Similar to the Bharathi *et al.* study which showed that the vegetative type of trauma was the most frequently occurring potential risk observed,

corneal injuries predisposing to corneal infections were revealed to be the most significant predictor in our investigation. Sugarcanes were the most frequent source of ocular injury among vegetal matters [23].

Seven of the seventeen effectively treated groups in the initial participants received just one injection, while six received two injections, and four received three. Patient failure number three received four injections. In 17 healed patients, the average number of doses was 2.57± 1.63. The size of the ulcer at presentations had a big impact on how well it responded to treatments. A higher chance of therapeutic failure was linked to larger ulcers. These results were also seen in the research by Kalaiselvi *et al.* [24].

In this investigation, individuals who attended sooner than later recovered more quickly and needed fewer injections. In addition, individuals with fewer infiltrates needed fewer injections.

If there is a hazard of corneal melts and perforations, Prakash *et al.* demonstrated in their research that intrastromal management of voriconazole is a secure and cost-effective technique for providing higher concentrations of the medication. They also demonstrated that using (0.05 - 0.1 ml) of voriconazole (50 µg/0.1 mL) assisted in the resolution of various fungal infectious diseases [25]. In this work, we established that intrastromal voriconazole use was safe at concentrations of 10 µg/mL to 1.5 mg/mL in water. Hardly long-term ocular damage was noticed after recurrent intrastromal injections of voriconazole (50 g/0.1 mL), which was well accepted. These results were also noted in the research of Kernt *et al.* [26].

Throughout a specific drug delivery method in our investigation, intrastromal voriconazole has the ability to achieve appropriate medication concentrations at the site of infections. A suitable dose of the medication was injected around the abscesses, creating a sufficient and long-lasting deposition around the lesions circumferences to prevent hyphae from spreading to the healthy corneal.

The second group in this research included five eyes required two injections, five eyes required three injections, and four eyes recovered with just one intracameral injection. The inflammation reaction was seen to wane in the four eyes that only needed one therapy following 2 days, and the hypopyon vanished within three and ten days after injections (mean, 5.21 ± 3.18 days).

The application of intracameral amphotericin B injections in the treatment of fungus keratitis was described by Garcia-Valenzuela *et al.* They discovered that all individuals had a favorable response, with complete eradication of corneal infections and hypopyons and no indications of corneal or lenticular damage. Amphotericin B injections were secure, according to our investigation. After receiving the injections, neither of our patients experienced systemically adverse effects from the medication [27].

According to Yilmaz *et al.*, the clinical dosage of amphotericin B that is advised for intracameral injections is ten to thirty grams in 0.1 to 0.2 mL. In our instances, intracameral injections up to 50 g/mL were administered, and a medicinal dosage was easily supplied without noticeably negative side effects [28]. According to a publication by Kuriakose *et al.*, all of our patients in both categories experienced significant elevations in the anterior chamber's reactivity and discomfort right away after injections [29]. In our research on eyes with fungal keratitis, hypopyon is typical. Hypopyon was discovered to be present in association with big infiltration size. 7.5% of the participants in our research had exhibiting VA of less than 6/60. This prevalence was considerably lower than what Garg *et al.* (71.6%) recorded [30].

The average recovery time was (21.29± 6.29) days, and the average following-up duration was (29.23 ± 6.41) days. Following recovery, the corneal depth was (385.29 ± 59.49) mm (414 µM~ 499 µM). The BCVA at the last follow-up was greater than the BCVA after restoration (P = 0.019), and the BCVA after restoration exhibited substantial improvements when compared to pre-treatments (P = 0.01).

In five eyes (12.5%), therapeutic penetration keratoplasty was done. There were two in the second category and three in the first. They had all previously experienced ocular injuries brought on by vegetative materials. At the time of diagnosis, all of them had been receiving topical antibiotics (Natamycin, Tobramycin +

Moxifloxacin, and Natamycin + Moxifloxacin + Voriconazoles). In a prospective trial on twelve eyes, Sharma N. *et al.* [31] showed a successfulness rate of more than 80%, Similar results were observed by Kalaiselvi *et al.* [32] who noted a 72% therapy successfulness rate in Tamil Nadu, India. In eighteen of the 25 eyes, the recovery had been effective. A success rate of 85 percentage points was achieved in our report's initial group when 17 out of 20 patients responded to intrastromal therapy. A 90 percent success rate was achieved in the second category, where Eighteen out of 20 patients reacted to intracameral amphotericin B therapy.

Conclusion

The treatment of fungal keratitis is still difficult. The causes for poor prognosis in fungal keratitis are compounded by newly emerging fungal infections and resistance to already available antifungal medications. For persistent deeply fungal corneal ulcers, intrastromal voriconazoles and intracameral amphotericin B seem to be a successful therapy option. Thus, it is concluded that in some individuals, intrastromal voriconazole may be administered as a replacement for fungal ulcers that do not heal. Subsequent identification of fungal species may facilitate which agent would be best added for dual therapy (amphotericin B for yeast; voriconazole for mold species) for treatment of severe or unresponsive disease might assist in lowering the possibility of problems, such as corneal perforations, necessitating therapeutic keratoplasty.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the article and agreed to be responsible for all aspects of this work.

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