Comparison of effectiveness of oral ketoconazole in deep keratomycosis and intracameral voriconazole- A comparative study

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ABSTRACT

Background:

Fungal keratitis, the world's second leading cause of blindness after cataracts, is one of the most common causes of ocular mycosis. The study's goal was to compare the efficacy of traditional topical, systemic, and intracameral voriconazole injections in treating keratomycosis visual and structural outcomes.

Material and methods

An observational study was conducted at a hospital on 45 patients with smear-positive fungal keratitis in 45 eyes. Patients were split into two groups: Systemic topical with oral ketoconazole 150 mg was given to Group I, while intracameral voriconazole 60 gm/0.1 mL was given to Group II.

Results:

Fusarium is the name given to the most common fungal organism. The mean final visual acuity (VA) in Groups I, II, and III was 1.15 0.32, 1.45 1.04, and 1.21 0.37 logMAR, respectively. The mean VA improvement was 0.44 0.06, 0.02 0.61, and -0.17 0.02 logMAR without statistical significance ($p = 0.8$). There was a significant difference in VA between the final postoperative follow-up period and baseline in Group I cases ($p = 0.0018$). There was no difference in VA between the final postoperative follow-up period and baseline in Group II ($p = 0.0561$) or Group III ($p = 0.1605$) cases. There was no statistically significant difference in time between the onset of hypopyon and the mean time to infection healing ($p = 0.1$). In each group, three cases were perforated, and keratoplasty was performed. Culture was not found in these perforated cases. The isolated organisms in the corneal buttons were identified as Aspergillus species ($n = 2$) and Fusarium species ($n = 4$).

Conclusion:

The VA differences between the three methods were not statistically significant, implying that none of the treatments was superior to the others (inter-group). There was, however, a significant difference in VA

between the final postoperative follow-up period and baseline in Group I (p = 0.0018). In Groups II (p = 0.0561) and III (p = 0.1605), there was no difference in VA between these time intervals. The Group I method is more effective for VA, according to within-group or intra-group analysis. The duration of intracameral voriconazole in the anterior chamber, the absence of hypopyon drainage, and the individual clinical response all contributed to the success rate of the method.
Key words: Voriconazole; Keratomycosis; Aspergillus;

Introduction

Microbial keratitis is the leading cause of blindness worldwide.[1] In developing countries, it is common, and both active and resolved infectious keratitis are significant indications for corneal transplantation. In India, fungal aetiology accounts for one-third of corneal ulcers. Fungal keratitis (FK) infection is more virulent/damaging than bacterial infection. Fungal keratitis is more likely than bacterial keratitis to perforate the cornea (OR = 4.95, 95% CI: 2.06-16.69). Ocular trauma has been identified as a risk factor for FK in developing countries.[2-8]

Voriconazole is the first second-generation broad-spectrum antifungal agent. It prevents fungal growth by inhibiting the enzyme cytochrome P475 14-a-demethylase (P450 14DM), which disrupts the close packing of phospholipid acyl chains. After oral administration, voriconazole is rapidly absorbed.[9, 10]

Material and methods

The present study was conducted on 85 patients in Tertiary Eye Care Center, India, from August 2018 to January 2019.

Each patient underwent a routine ophthalmic examination. The presenting complaints' history, trauma, treatment received, and so on were all documented. Slit-lamp microscopy was used to determine the size of the corneal ulcer, the depth of the infiltrate, the endothelial plaque, the satellite lesions, the size of the hypopyon, the nature of the hypopyon, and the presence of a cataract. To diagnose chronic dacryocystitis, syringing was used. 90D biomicroscopy and, if necessary, B-scan ultrasonography were used to evaluate the posterior segment. A thorough examination was carried out to detect hypertension, diabetes, and immunocompromised status. Microbiological tests were performed on the corneal ulcer. Based on the patient's history, clinical features, and microbiological investigations, including Gram staining, the fungal corneal ulcer was diagnosed. Sabouraud dextrose agar (SDA) was used for fungal culture.

Statistical analyses

Computer software was used to perform statistical analyses (SPSS version 20 and primer). The qualitative data were expressed as percentages and proportions, while the quantitative data were expressed as means and standard deviations.

RESULTS

Distribution (%) of patients according to age group and gender

S. No	Age group	Males	Females	Total
1.	10-20	3(10%)	1(15%)	1(8%)
2.	21-30	3(10%)	7(10%)	1(2%)
3.	31-40	4(20%)	4(25%)	3(40.%)

4.	41-50	8(25%)	8(30%)	14(30%)
5.	51-60	2(5%)	5(16%)	8(15%)
6.	61-70	9(30%)	4%	5(15%)
Total		29(100%)	26(100%)	32(100%)

Corneal ulcer location

S. No.	Location	No. of patients
1.	Central	18(70%)
2.	Paracentral	20(30%)
3.	Peripheral	00
4.	Total	28 (100%)

The percentage of patients who healed their ulcers after intrastromal voriconazole injection was distributed (%).

S. No	Weeks	No. of cases
1.	4 weeks	8(13.3%)
2.	6 weeks	5(56.9%)
3.	8 weeks	7(06.2%)
4.	Perforation of ulcer after 2 weeks of treatment.	1(18%)
5.	Did not come to follow up after one week treatment in hospital.	4(5.6%)

DISCUSSION

Voriconazole is a triazole antifungal agent that causes fungal death by inhibiting lanosterol 14-demethylase in the fungal cell membrane, disrupting the conversion of lanosterol to ergosterol and thus affecting the stability of the fungal cell membrane. It is used to treat Aspergillus, Candida, and Fusarium fungal infections, as well as fungi that are resistant to fluconazole, itraconazole, or amphotericin B. Voriconazole is a concentration-dependent drug, which means that the stronger the antifungal effect, the higher the concentration of the drug that reaches the lesion. The concentration cannot be harmful to the cornea at the same time. Voriconazole's ability to reach corneal tissue is still limited due to ocular drug delivery challenges, despite having higher permeability in the cornea stroma than other antifungal agents. As a result, treatment is prolonged, and the likelihood of recurrence is high. Fungal infection causes chronic inflammatory cell and cytokine infiltration, which usually results in stromal scarring, progressive corneal thinning and perforation, or even fungal endophthalmitis.

Several researchers used the corneal stroma injection procedure to increase the local drug concentration in the corneal lesion and discovered that it was effective in resolving the issue of antifungal agent poor penetrability into the corneal stroma. Despite evidence that intrastromal voriconazole injection increases drug concentrations in the cornea stroma, therapeutic efficacy has been questioned. These discrepancies could be attributed to differences in injection methods used in different studies, resulting in variable drug concentration and distribution in the corneal stroma.[9,10] Concurrently, some studies suggest that intrastromal injections in fungal keratitis may increase the risk of corneal perforation. The tricyclic

corneal stroma injection (TCSI) procedure for intrastromal injection of voriconazole was developed to address this issue.

Due to factors such as poor penetration, surface toxicity, and a limited spectrum of topical antifungal agents, deep fungal keratitis is difficult to treat. To address the issue of low drug penetration, modalities for targeted drug delivery have recently been investigated. Antifungal drugs were injected intrastromally to achieve optimal intracorneal concentrations. Previously, intrastromal amphotericin b was used to treat recalcitrant fungal ulcers.[11] Amphotericin b, on the other hand, has been linked to a variety of side effects, including surface toxicity, retinal toxicity, and others. Newer agents, such as voriconazole, have demonstrated superior efficacy against filamentous fungi due to lower mean inhibitory concentration (MIC) and improved penetration. Furthermore, when compared to amphotericin b, the systemic side effects are less severe. Recent research has supported the use of intrastromal voriconazole in the treatment of nonhealing mycotic infections.[12] Subjects who had not responded to conventional topical antifungal therapy after two weeks were scheduled for an intrastromal injection in this study. The drug was injected around the infiltration's circumference, resulting in a flood of drug deposits around the lesion. The drug concentration in 0.1 ml was 50 mcg.

Fungal keratitis is an infectious disease that can cause blindness. Current antifungal drugs fall into four categories: polyenes, imidazoles, triazoles, and luorinated pyrimidines. These drugs can be given intravenously, topically, or orally. They do, however, have a low penetration, a limited spectrum, ocular surface toxicity, a modest clinical response, and a longer course of therapy. Amphotericin and natamycin are the two most commonly used topical medications. Nonetheless, resistance to amphotericin B is increasing. Itraconazole and voriconazole are the most commonly used systemic therapies for filamentous ulcers. Due to ineffective medical therapy and increasing thinning with impending perforation, 15-15-27% of patients with severe keratitis require surgical treatment (such as keratoplasty, evisceration, or enucleation).[13-17]

Sun et al. found that corneal debridement combined with intrastromal voriconazole was safe and effective in 14 patients with recalcitrant fungal keratitis. Prakash et al. administered voriconazole intrastromal injections to three patients, all of whom had their infections under control. A similar study by Konar et al. found that 14 of 20 patients responded positively, and the lesion was successfully treated. In such patients, we believe that careful intrastromal delivery of antifungal medications, in conjunction with topical therapy, may be extremely beneficial. Advantages of Intrastromal Voriconazole Injection: I A high healing rate of resistant mycotic fungal keratitis. (ii) Patient compliance with other topical drugs in terms of duration and dosage is reduced because the medication is administered as a depot.[18]

Pattern recognition receptors (PRRs) on host epithelial and immune cells recognise fungi when they come into contact. Toll-like receptors (TLRs) such as TLR2 and TLR4 are PPRs. They are C-type Lectin receptors as well (CLRs, including Dectin-1, Dectin-2 and Mincle). Dectin-1 recognises -glucan in the fungal cell wall, whereas Dectin-2 and Mincle recognise mannan in the fungal cell wall.[19,20] During fungal keratitis, TLR has been shown to detect Candida albicans and Aspergillus fumigatus interactions.

TLRs activated in the corneal epithelium cause the production of CXC chemokines as well as the recruitment of neutrophils (which make up more than 90% of the infiltrating cells). Neutrophils are the primary source of mature interleukin-1 (IL-1) and acidic mammalian chitinase (AMCase) in corneas, both of which can inhibit hyphal growth.[21, 22] Increased production of reactive oxygen species (ROS) in response to increased levels of IL-1, TLR4, Dectin-1, and LOX-1 aids in fungal killing.

CONCLUSIONS

Intrastromal injection of voriconazole combined with topical voriconazole effectively reduced infiltration size and controlled the infection in patients with Fusarium keratitis. However, continuing to apply the topical medication is essential for a successful treatment outcome.

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