Journal of Cardiovascular Disease Research
ISSN: 0975-3583,0976-2833, Issue 8 Vol 4, 2017

TOPICAL ADMINISTRATION OF 1% POSACONAZOLE TREATMENT IN INSTANCES OF FUNGAL KERATOSIS

Dr. Vaghela Mayurkumar Dilipsinh

Associate Professor, Department of Ophthalmology, Gouri Devi Institute of Medical Sciences & Hospital, Durgapur (W.B)

Email - mvaghela.76@gmail.com

==========

ABSTRACT

Background: Posaconazole has demonstrated encouraging clinical outcomes in patients with fungal keratitis that is resistant to treatment.

Aim: The purpose of this research was to evaluate the clinical response to topical administration of 1% posaconazole treatment in instances with fungal keratosis that were resistant.

Methods: The research evaluated 140 eyes with refractory fungal keratitis, 70 of which were treated with PCZ (posaconazole) at 1% posaconazole therapy and 70 of which were treated with traditional antifungal therapy. The study evaluated visual acuity, ASCOT, clinical photography, thorough slit lamp biomicroscopy, demographic information, therapy details, and weekly for weeks 1, 2, 3, and 4 after treatment beginning. Clinical evaluation included keratitis severity grade, healing response, and healing time. Testing for antifungal susceptibility was also conducted.

Results: In terms of ulcer features, the PCZ group's healing time was 27.11±5.6 days, whereas the conventional care groups were 26.39±4.79 days. This difference was statistically not significant (p=0.58). Hypopyon, endothelial plaque, stromal infiltration, and epithelial ulcers all showed similar non-significant differences (p=0.08, 0.33, 0.44, and 0.58, respectively). TPK (therapeutic keratoplasty) was required for the healing response in 14.28% (n=10) of the PCZ group and 20% (n=14) of the standard care group, with a statistically insignificant difference (p=0.52). Similar non-significant findings (p=0.74 and 0.63, respectively) were seen for delayed healing and healing in the PCZ and conventional groups.

Keywords: Posaconazole, mycotic keratitis, fungal keratitis, and antifungal susceptibility testing

INTRODUCTION

Accurately identifying the causal agent is essential for the successful treatment of fungal corneal infections. For ocular fungal infections, azole and polyene-based pharmacotherapy are viable antimycotic treatments. Voriconazole's superior in-vitro profile over natamycin has supported its usage as the preferred medication for deep mycotic keratitis. Posaconazole, or PCZ, has a wide range of antimycotic effectiveness against a variety of newly discovered corneal pathogenic mycotic organisms. It has been discovered that PCZ-extended spectrum works well against filamentous fungus, yeasts, andazole-resistant Candida species, as well as the majority of Fusarium species.[1]

When treating instances of resistant mycotic keratitis brought on by Paecilomyces and Fusarium, oral PCZ at a dosage of 500–600 mg once day has been shown to be effective. According to reports, PCZ treatment works well for recalcitrant Fusarium keratitis that is resistant to traditional antifungal medications. According to reports, PCZ and amphotericin work in concert to combat filamentous fungus (Absidia corymbifera keratitis). According to recent evidence, PCZ micellar medication delivery is effective in treating fungal infections of the eyes. Nevertheless, there is no study with a

larger sample size, and these are isolated cases that demonstrate the effectiveness of PCZ in treating fungal keratitis.[2]

PCZ has the lowest MIC (minimum inhibitory concentration) against common fungal keratitis isolates, according to recent literature data. Common corneal pathogenic fungi are known to show diversity in sensitivity to conventional antifungal drugs. Additionally, it has been found that topical PCZ, which has therapeutic corneal concentrations that make it suitable for corneal fungal infections, is more effective than intrastromal injections of high concentrations for extended periods of time.[3]

It is alarming to see resistance trends in several invading fungus species. Since azoles are often used fungicides to reduce corneal pathogenic fungus, the rise in azole resistance is concerning. Rhizopus, Mucor, Curvularia, aletrnaria, Fusarium spp., and Aspergillus spp. are among the common corneal pathogenic fungi for which antifungal susceptibility testing for the commonly used antifungal agents and susceptibility patterns to newer antifungal agents such as caspofungin, micafungin, and posaconazole have demonstrated good results for in-vitro posaconazole response with low MIC levels.[4]

Prior to administering medications, antifungal drug susceptibility testing has become essential due to the rise in reported fungus resistance to antifungal treatment agents. The widespread use of empirical treatment to treat fungal ulcers in the absence of susceptibility data may be a contributing reason to the higher morbidity rate of severe keratomycosis. Treatment failure is more likely when multiple triazole resistance is on the rise. The restricted availability of topical antifungal medicines, the emergence of resistance to conventional antimycotic treatments, and varying results to antifungal susceptibility tests in fungal keratitis. Investigating the clinical response to more recent antimycotic medications is justified.[5]

The current investigation evaluated the clinical response in refractory instances of fungal keratosis following topical administration of 1% posaconazole treatment, given the encouraging clinical and in-vitro findings demonstrated by PCZ usage in fungal keratitis.

MATERIALS AND METHODS

Following topical administration of 1% posaconazole treatment, the current longitudinal prospective research sought to determine the clinical response in refractory instances of fungal keratosis. The research participants came from the Institute's Department of Ophthalmology. Before participating in the study, all participants and school officials gave their verbal and written informed consent.

Seventy eyes with fungal keratitis who tested positive for fungal hyphae on corneal scraping/confocal microscopy imaging for more than three weeks were chosen as the PCZ treatment group and given topical 1% PCZ therapy. As the traditional treatment group, these eyes were contrasted with seventy controls who had culture-positive refractory fungal keratitis and were receiving traditional antifungal medication.

Every participant had corneal scraping at inclusion and had non-healing fungal keratitis that lasted longer than three weeks. The topical care for participants who agreed to PCZ medication was changed to 1% topical PCZ every two hours, while those who refused were given a standard antifungal regimen consisting of 5% natamycin and 0.1% voriconazole every two hours.

Subjects with severe and moderate-grade refractory keratitis lasting more than two weeks, with confocal microscopy hyphae/fungal culture/corneal smear fungal hyphae positive, who were willing to participate in the study, were the study's inclusion criteria. Participants who did not volunteer to

participate in the trial, those with a history of confocal microscopy hyphae-negative fungal keratitis, those with a negative KOH mount smear, and those with a known allergy to any topical antimycotic or other medication were excluded. Three milliliters of topical 1% PCZ eye drop with a pH of 6.91 were administered, and participants were instructed to keep it out of direct sunlight.

In addition to evaluating demographic information, all individuals underwent complete slit lamp biomicroscopy for clinical features, visual acuity, and treatment details, as well as anterior segment optical coherence tomography (ASOCT) at recruitment and weekly (weeks 1, 2, 3, and 4 following treatments beginning). For clinical evaluation, participants who needed therapeutic keratoplasty were evaluated based on their keratitis severity grade, healing time (endothelial plaque/hypopyon, stromal infiltrate, and epithelial infiltration), healing response as healed (<3 weeks), delayed (>3 weeks), and treatment failure. All individuals received carboxymethylcellulose as an adjuvant topical lubricant three times a day, with the exception of those receiving mydriatics and antiglaucoma medication.

Primary microscopy and fungal culture were included of the microbial evaluation. Fungal elements were detected in ocular tissues using primary microscopy using a 10% KOH mount. LPCB (Lacto Phenol Cotton Blue) mounts and slide culture were used to evaluate any growth that occurred during the 14-day incubation period on Saboraud's dextrose agar slants. Posaconazole (P), itraconazole (I), voriconazole (V), amphotericin B (A), and natamycin (N) were tested for antifungal susceptibility using E-strip at doses of N: 0.016–256 μg/mL; A: 0.002–32; V: 0.002–32 μg/mL; I: 0.002–32 μg/mL; F: 0.016–256 μg/mL; P: 0.002–32 μg/mL. When full epithelial healing was observed without fluorescein staining and infiltrate resolution to scar, medical therapy was deemed effective.

A 20% reduction in ulcer size, a stromal infiltrate that has not healed, epithelial repair without fluorescein staining and infiltrate resolution, and the need for ongoing medical treatment were all regarded indicators of delayed healing. When there was no epithelial healing, a perforation, an increase in infiltration, and a need for therapeutic keratoplasty or surgical intervention, medical therapy was deemed unsuccessful.

ANOVA, the chi-square test, the student's t-test, Fisher's exact test, the Mann Whitney U test, and SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk, NY, USA) were used to statistically analyze the collected data. A p-value of less than 0.05 was regarded as the significance level.

RESULTS

Following topical administration of 1% posaconazole treatment, the current longitudinal prospective research sought to determine the clinical response in refractory instances of fungal keratosis. 140 eyes with refractory fungal keratitis were evaluated in the trial; 70 were treated with PCZ (posaconazole) at 1% posaconazole therapy, and 70 received traditional antifungal medication. The study evaluated visual acuity, ASCOT, clinical photography, thorough slit lamp biomicroscopy, demographic information, therapy details, and weekly for weeks 1, 2, 3, and 4 after treatment beginning. Clinical evaluation included keratitis severity grade, healing response, and healing time. Testing for antifungal susceptibility was also conducted.

When evaluating the visual acuity of two study groups, it was observed that 40% (n=28) of the controls had PL (perception of light) at 0 weeks, 40% (n=28) had HMCF (hand movements close to the face) at 0 weeks and 8.57% (n=6) at 4 weeks, 5.71% (n=4) had FCCF (finger counting close to face) at 0 weeks and 20% (n=14) at 4 weeks, and 71.43% (n=50) had >FC 1m at 4 weeks. For example, 37.14% (n=26) of the participants had PL at 0 weeks, 62.86% (n=4) had HMCF at 0 weeks

and 14.28% (n=10) at 4 weeks, 2.8% (n=2) had FCCF at 0 and 22.85% (n=16) at 4 weeks, and 62.855 (n=44) had >FC 1m at 4 weeks (Table 1).

According to the research's findings, the healing time for ulcer features in the study participants was 27.11±5.6 days in the PCZ group and 26.39±4.79 days in the traditional care group. This difference was statistically not significant (p=0.58). Hypopyon, endothelial plaque, stromal infiltration, and epithelial ulcers all showed similar non-significant differences (p=0.08, 0.33, 0.44, and 0.58, respectively).

TPK (therapeutic keratoplasty) was required for the healing response in 14.28% (n=10) of the PCZ group and 20% (n=14) of the standard care group, with a statistically insignificant difference (p=0.52). Similar non-significant findings (p=0.74 and 0.63, respectively) were seen for delayed healing and healing in the PCZ and conventional groups (Table 2).

Penicillin's susceptibility to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin) was evaluated in 100%, 0, 90%, 80%, 10%, 100%, and 8% of the research participants (n=4). Altemaria had susceptibility to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin) in 100%, 0, 0, 100%, 0, 0, and 12% (n=6) subjects, Cladosporium had susceptibility to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin) in 90.6%, 66.6%, 66.6%, 66.6%, 100%, 100%, and 8% (n=4) subjects, A. niger had sensitivity to P, F, I, V, and A in 100%, 0, 100%, 100%, 100%, and 33.4% subjects, A. flavus had sensitivity to P, F, I, V, A, and N in 89.7%, 13.4%, 84.7%, 90.4%, 40%, 55.4%, and 32% (n=16) subjects, and fusarium had sensitivity to P, F, I, V, A, and N in 88%, 13.4%, 13.4%, 65.6%, 35%, 90.3%, and 40% (n=20) subjects respectively in PCZ group (Table 3).

Rhizopus exhibited sensitivity to P, F, I, V, A, and N in 90%, 0%, 33%, 30%, 60%, 80%, and 2.85% (n=2) of the individuals in the usual therapy group, respectively. P, F, I, V, A, and N were the antibiotics to which 100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) of the individuals were sensitive. 100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) of the participants were sensitive to P, F, I, V, A, and N, respectively. 96.6%, 66.2%, 66.6%, 66.6%, 80%, 90%, and 5.71% (n=4) of the participants were sensitive to P, F, I, V, A, and N, respectively. In 100%, 10%, 100%, 96%, 91%, and 92% of the patients, A. furigatus exhibited sensitivity to P, F, I, V, and A, respectively.

In 100%, 10%, 100%, 95%, 90%, and 33.4% of the patients, A. niger exhibited sensitivity to P, F, I, V, and A, respectively. In 86.7%, 13.4%, 88.7%, 93.4%, 30%, and 63.4% of patients, A. flavus exhibited sensitivity to P, F, I, V, and A, respectively. In 90%, 18.4%, 15.4%, 68.6%, 60%, 89.3%, and 42.85% (n=30) participants, respectively, Fusarium exhibited sensitivity to P, F, I, V, A, and N (Table 3).

DISCUSSION

According to the study's findings, when evaluating the visual acuity of two groups of study participants, 40% (n=28) of the controls had PL (perception of light) at 0 weeks, 40% (n=28) had HMCF (hand movements close to the face) at 0 weeks and 8.57% (n=6) at 4 weeks, 5.71% (n=4) had FCCF (finger counting close to face) at 0 weeks and 20% (n=14) at 4 weeks, and 71.43% (n=50) had >FC 1m at 4 weeks.

In these instances, 37.14% (n=26) of the individuals had PL at 0 weeks, 62.86% (n=4) had HMCF at 0 weeks and 14.28% (n=10) at 4 weeks, 2.8% (n=2) had FCCF at 0 and 22.85% (n=16) at 4 weeks,

and 62.855 (n=44) had >FC 1m at 4 weeks. These findings were in line with earlier research by Prajna NV et al. (2016) and Kredics L et al. (2015), where the authors also found visual acuity values equivalent to the current study.

In terms of ulcer features, the PCZ group's healing time was 27.11±5.6 days, whereas the conventional care group's was 26.39±4.79 days. This difference was statistically not significant (p=0.58). Hypopyon, endothelial plaque, stromal infiltration, and epithelial ulcers all showed similar non-significant differences (p=0.08, 0.33, 0.44, and 0.58, respectively). TPK (therapeutic keratoplasty) was required for the healing response in 14.28% (n=10) of the PCZ group and 20% (n=14) of the standard care group, with a statistically insignificant difference (p=0.52). Similar non-significant findings (p=0.74 and 0.63, respectively) were seen for delayed healing and healing in the PCZ and conventional groups. These findings aligned with those of Lalitha P et al. (2007) and Nayak N et al. (2011), whose research found ulcer features similar to those of the current investigation.

Penicillin's susceptibility to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin) was evaluated in 100%, 0, 90%, 80%, 10%, 100%, and 8% of the research participants (n=4).

In 100%, 0, 0, 100%, 0, 0, and 12% (n=6) of the individuals, Altemaria were susceptible to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin). In 90.6%, 66.6%, 66.6%, 66.6%, 100%, 100%, and 8% (n=4) of the individuals, Cladosporium was susceptible to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin). In individuals that were 100%, 100%, 100%, 100%, and 33.4% sensitive to P, F, I, V, and A, A. niger Fusarium was sensitive to P, F, I, V, A, and N in 88%, 13.4%, 13.4%, 65.6%, 35%, 90.3%, and 40% (n=20) of the PCZ group, whereas A. flavus was sensitive to P, F, I, V, A, and N in 89.7%, 13.4%, 84.7%, 90.4%, 40%, 55.4%, and 32% (n=16) of the individuals.

These results were consistent with those of Castillo Castañeda A et al. (2010) and Gueudry J et al. (2011), who also demonstrated antifungal susceptibility in study subjects on 1% PCZ that was equivalent to the current study.

Rhizopus was also shown to be sensitive to P, F, I, V, A, and N in 90%, 0%, 33%, 30%, 60%, 80%, and 2.85% (n=2) of the participants in the usual therapy group. P, F, I, V, A, and N were the antibiotics to which 100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) of the individuals were sensitive. 100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) of the participants were sensitive to P, F, I, V, A, and N, respectively.

96.6%, 66.2%, 66.6%, 66.6%, 80%, 90%, and 5.71% (n=4) of the participants were sensitive to P, F, I, V, A, and N, respectively. In 100%, 10%, 100%, 96%, 91%, and 92% of the patients, A. furigatus exhibited sensitivity to P, F, I, V, and A, respectively. In 100%, 10%, 100%, 95%, 90%, and 33.4% of the patients, A. niger exhibited sensitivity to P, F, I, V, and A, respectively. In 86.7%, 13.4%, 88.7%, 93.4%, 30%, and 63.4% of patients, A. flavus exhibited sensitivity to P, F, I, V, and A, respectively. In 90%, 18.4%, 15.4%, 68.6%, 60%, 89.3%, and 42.85% (n=30) of the individuals, Fusarium was sensitive to P, F, I, V, A, and N, respectively.

These findings were consistent with those of Vanathi M et al. (12) and Durgun ME et al. (13), who found that antifungal susceptibility in participants receiving conventional medication was similar to the findings of the current investigation.

CONCLUSION

Within its limitations, the present study concludes that 1% topical posaconazole therapy in subjects with refractory fungal keratitis was comparable to the conventional antimycotic agents with MIC-50 lower against common pathogenic fungi in comparison to voriconazole, amphotericin B, and natamycin.

REFERENCES

1. Hariprasad SM, Mieler WF, Lin TK, Sponsel WE, Graybill JR. Voriconazole in the treatment of fungal eye infections: A review of current literature. Br J Ophthalmol 2008;92:871–8.
2. Sponsel WE, Graybill JR, Nevarez HL, Dang D. Ocular and systemic posaconazole (SCH-56592) treatment of invasive Fusarium solani keratitis and endophthalmitis. Br J Ophthalmol 2002;86:829-30.
3. Ahirwar LK, Sheba E, Jakati S, Jayasudha R, Padakandla SR, Bagga B, et al. Elucidating the clinical, microbiological and molecular diagnostic aspects of Macrophomina phaseolina keratitis. Med Mycol 2022. doi: 10.1093/mmy/ myac024
4. Kaufmann C, Arnold M, Schipf A, Bruderer VL, Iselin KC. Tintelnotia destructans Keratitis: A clinicopathological report and review of the literature. Cornea 2021;40:380-2.
5. Lakhani P, PatilA, Majumdar S. Challenges in the polyene- and azole-based pharmacotherapy of ocular fungal infections. J Ocul Pharmacol Ther 2019;35:6-22.
6. Prajna NV, Lalitha P, Rajaraman R, Krishnan T, Raghavan A, Srinivasan M, et al. Changing azole resistance: A secondary analysis of the MUTT I randomized clinical trial. JAMA Ophthalmol 2016;134:693-6.
7. Kredics L, Narendran V, Shobana CS, Vágvölgyi C, Manikandan P; Indo-Hungarian Fungal Keratitis Working Group. Filamentous fungal infections of the cornea: A global overview of epidemiology and drug sensitivity. Mycoses 2015;58:243–60.
8. Lalitha P, Shapiro BL, Srinivasan M, Prajna NV, Acharya NR, Fothergill AW, et al. Antimicrobial susceptibility of Fusarium, Aspergillus, and other filamentous fungi isolated from keratitis.Arch Ophthalmol 2007;125:789-93.
9. Nayak N, Satpathy G, Prasad S, Titiyal JS, Pandey RM, Vajpayee RB. Molecular characterization of drug-resistant and drug-sensitive Aspergillus isolates causing infectious keratitis. Indian J Ophthalmol 2011;59:373–7.
10. Castillo-Castañeda A, Cañas-Duarte SJ, Guevara-Suarez M, Guarro J, Restrepo S, Celis Ramírez AM. Transcriptional response of Fusarium oxysporumand Neocosmospora solani challenged with amphotericin B or posaconazole. Microbiology (Reading) 2020;166:936-46.
11. Gueudry J, Le Goff L, Lamoureux F, Pereira T, Levefre S, Razakandrainibe R, et al. Corneal pharmacokinetics of voriconazole and posaconazole following intrastromal injection and posaconazole eye drops instillation in rats. Curr Eye Res 2020;45:1369-72.
12. Vanathi M, Naik R, Sidhu N, Ahmed NH, Gupta N, Tandon R. Evaluation of antifungal susceptibility and clinical characteristics in fungal keratitis in a tertiary care center in North India. Indian J Ophthalmol 2022;70:4270-83.

13. Durgun ME, Kahraman E, Hacıoğlu M, Güngör S, Özsoy Y. Posaconazole micelles for ocular delivery: In vitro permeation, ocular irritation and antifungal activity studies. Drug Deliv Transl Res 2022;12:662-75.

Groups	PL n (%)		HMCF n (%)		FCCF n (%)		>FC 1m n (%)	
	0 week	4 weeks	0 week	4 weeks	0 week	4 weeks	0 week	4 weeks
Controls	28 (40)	-	28 (40)	6 (8.57)	4(5.71)	14 (20)	-	50(71.43)
Cases	26(37.14)	-	42(62.86)	10(14.28)	2 (2.8)	16(22.85)	-	44(62.85)

Table 1: Visual acuity in two groups of study subjects

Ulcer characteristics	PCZ (n=70)	Conventional management (n=70)	p-value
Healing time (days)			
Total healing time	27.11±5.6	26.39±4.79	0.58
Hypopyon	16±4.53	17±5.55	0.08
Endothelial plaque	16±3.68	19±3.38	0.33
Stromal infiltrate	21.14±4.79	22.18±4.25	0.44
Epithelial ulcer	27.11±5.6	26.39±4.79	0.58
Healing response in study subjects n (%)			
TPK (therapeutic keratoplasty)	10 (14.28)	14 (20)	0.52
Delayed healing	6 (8.5)	4 (5.71)	0.74
Healed	54 (77.14)	52 (74.28)	0.63

Table 2: Ulcer characteristics in study subjects

Fungi isolated		No of eyes (n)	P	F	I	V	A	N
PCZ group (n=50) %	Penicillin	100	0	90	80	10	100	4 (8%)
	Altemaria	100	0	0	100	0	0	6 (12)
	Cladosporium	90.6	66.6	66.6	66.6	100	100	4 (8)
	A. Niger	100	0	100	100	100	33.4	
	A. flavus	89.7	13.4	84.7	90.4	40	55.4	16 (32)
	Fusarium	88	13.4	13.4	65.6	35	90.3	20 (40)
Conventional treatment (n=50)	Rhizopus	90	0	33	30	60	80	2 (2.85)
	Penicillin	100	10	80	90	40	100	4 (5.71)
	Altemaria	100	10	80	90	40	100	4 (5.71)
	Cladosporium	96.6	66.2	66.6	66.6	80	90	4 (5.71)
	A. furigatus	100	10	100	96	91	92	-
	A. niger	100	10	100	95	90	33.4	-
	A. flavus	86.7	13.4	88.7	93.4	30	63.4	-
	Fusarium	90	18.4	15.4	68.6	60	89.3	30(42.85)

Table 3: Antifungal susceptibility in two groups of study subjects