Section: Ophthalmology

Original Research Article

EVALUATING THE CLINICAL RESPONSE IN REFRACTORY CASES OF FUNGAL KERATOSIS AFTER TOPICAL APPLICATION OF 1% POSACONAZOLE THERAPY

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Received : 26/04/2025
Received in revised form : 08/06/2025
Accepted : 30/06/2025

Keywords:
Anti fungal susceptibility testing, fungal keratitis, mycotic keratitis, posaconazole.

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DOI: 10.47009/jamp.2025.7.4.66

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (4); 358-362

ABSTRACT

Background: As posaconazole has shown promising clinical results in subjects with refractory fungal keratitis. As response to antifungal susceptibility testing in fungal keratitis is varied for common topical antifungal agents, there is increasing resistance to common antimycotic agents with limited topical antifungal agent availability. There us need to explore clinical response for newer antimycotic agents. The present study was aimed to assess the clinical response in refractory cases of fungal keratosis after topical application of 1% posaconazole therapy. **Materials and Methods:** The study assessed 140 eyes of refractory fungal keratitis where 70 were taken for PCZ (posaconazole) treatment for 1% posaconazole therapy and 70 for conventional antifungal therapy. Parameters assessed in the study were demographic data, treatment details, clinical photography, comprehensive slit lamp biomicroscopy, visual acuity at recruitment and weekly for weeks 1, 2, 3, and 4 following treatment initiation. Clinical assessment was grade of keratitis severity, healing time, and healing response. Anti fungal susceptibility testing was also done. **Result:** For ulcer characteristics in study subjects, healing time was 27.11±5.6 days in PCZ and 26.39±4.79 days in conventional management group depicting statistically non-significant difference with p=0.58. Similar non-significant difference was seen for hypopyon, endothelial plaque, stromal infiltrate, and epithelial ulcers with p=0.08, 0.33, 0.44, and 0.58 respectively. For healing response in study subjects, TPK (therapeutic keratoplasty) was needed in 14.28% (n=10) subjects in PCZ and 20% (n=14) subjects in conventional management group showing statistically non-significant difference with p=0.52. Similar non-significant results were seen for delayed healing and healing in PCZ and conventional group with p=0.74 and 0.63 respectively. **Conclusion:** 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.

INTRODUCTION

Successful management of fungal corneal infection is governed by accurate identification of causative agent. Azole and polyene-based pharmacotherapy include the available antimycotic therapy for ocular fungal infections. Superior in-vitro voriconazole profile compared to natamycin has advocated voriconazole use as drug of choice in deep mycotic keratitis. PCZ (posaconazole) has a broad spectrum of antimycotic activity including various emerging cornea pathogenic mycotic organisms. PCZ-extended spectrum has been found to be efficacious against majority of Fusarium spp., andazole resistant Candida species (spp.), filamentous fungi, and yeasts.[1]

Oral PCZ as 500-600mg daily dose once a day is reported to be efficacious in recalcitrant mycotic keratitis cases caused by Paecilomyces and Fusarium. PCZ therapy is reported to be efficacious in recalcitrant Fusarium keratitis resistant to conventional antifungal drugs. PCZ and amphotericin have been reported to be synergistic against filamentous fungi (Absidia corymbifera keratitis). Recent data has reported PCZ micellar drug delivery as efficacious in managing ocular fungal infections. However, these are isolated reports

ISSN (O): 2687-5365; ISSN (P): 2753-6556

that support success with PCZ in fungal keratitis with no study with larger sample size.[2]

Recent literature data has reported that there are common corneal pathogenic fungi that are known to exhibit variability in susceptibility to routine antifungal agents with PCZ having lowest MIC (minimum inhibitory concentration) against common fungal keratitis isolates. It is also reported that high concentration for long duration by intrastromal injections has low efficacy for PCZ compared to topical PCZ having therapeutic corneal concentrations making it useful for corneal fungal infections.[3]

Resistance patterns in various invasive fungal species are concerning. Increasing azole resistance is alarming as azoles have commonly used fungicides for controlling corneal pathogenic fungi. Using antifungal susceptibility testing for the commonly used antifungal agents and susceptibility pattern to newer antifungal agents including caspofungin, micafungin, and posaconazole have shown good results for in-vitro posaconazole response with low MIC levels for various common corneal pathogenic fungi including Rhizopus, Mucor, Curvularia, aletrnaria, Fusarium spp., and Aspergillus spp.[4]

With increased reported resistance of fungi to antifungal therapeutic agents, antifungal drug susceptibility testing has become vital before administration of drugs being use. Common practice of managing fungal ulcers using empirical therapy without susceptibility data can be one of the contributing factors to increased severe keratomycosis morbidity. An increasing trend for multiple triazole resistance results in increased treatment failure risk. With different responses on antifungal susceptibility testing in fungal keratitis response to the common topical antifungal agents, limited availability of topical antifungal agents, and emerging resistance to common antimycotic agents. It is warranted to explore clinical response to newer antimycotic agents.[5]

As promising clinical and in-vitro results are shown with PCZ use in fungal keratitis, the present study assessed the clinical response in refractory cases of fungal keratosis after topical application of 1% posaconazole therapy.

MATERIALS AND METHODS

The present longitudinal prospective study was aimed to the clinical response in refractory cases of fungal keratosis after topical application of 1% posaconazole therapy. The study was done at Department of Ophthalmology and Department of Microbiology, Rajarshi Dasrath Autonomous Medical College Ayodhya, Uttar Pradesh. Verbal and written informed consent were taken from all the subjects and school authorities before study participation.

The study assessed 70 eyes having fungal keratitis with fungal hyphae positivity on corneal scraping/confocal microscopy imaging of greater than 3 weeks of duration were recruited as the PCZ treatment group for topical 1% PCZ therapy. These eyes were compared with 70 controls with culture positive refractory fungal keratitis on conventional antifungal therapy as the conventional treatment group.

All the subjects had non-healing fungal keratitis greater than 3 weeks duration and underwent corneal scraping at inclusion. Subjects that were willing for PCZ therapy, topical management was altered to 1% topical PCZ every 2 hours and subjects not willing were placed on conventional antifungal treatment with 0.1% voriconazole and 5% natamycin every two hours.

The inclusion criteria for the study were subjects with refractory keratitis of severe and moderate grade of >2 weeks duration, aged >12 years, willing to participate in the study with confocal microscopy hyphae/ fungal culture positive/ corneal smear fungal hyphae positive. Exclusion criteria for the study were subjects that did not give consent for study participation, confocal microscopy hyphae negative fungal keratitis cases, KOH mount smear negative, and subjects with known allergy to any topical antimycotic or other drugs.

Topical 1% PCZ was dispensed as 3ml eye drop with pH 6.91 and subjects were advised to place it away from sunlight. In all the subjects, demographic data was assessed along at recruitment and weekly (weeks 1, 2, 3, and 4 after treatment initiation), comprehensive slit lamp biomicroscopy for clinical characteristics, visual acuity, and treatment details. For clinical assessment, severity grade of keratitis, healing time (endothelial plaque/ hypopyon, stromal infiltrate, and epithelial infiltrate), healing response as healed (<3 weeks), delayed (>3 weeks), and treatment failure was considered for subjects that required therapeutic keratoplasty). Adjuvant topical lubricant given was carboxymethylcellulose thrice daily for all subjects except antiglaucoma therapy and mydriatics.

Microbial assessment included fungal culture and primary microscopy. Primary microscopy for corneal specimens was done with 10% KOH mount where fungal element presence was seen. Culture was done on Saboraud's dextrose agar slants incubated for 14 days and any growth was assessed using LPCB (Lacto Phenol Cotton Blue) mounts and slide culture. AFST (Anti fungal susceptibility testing) was done with E-strip for posaconazole (P), itraconazole (I), voriconazole (V), amphotericin B (A), and natamycin (N) using concentrations of N: 0.016–256 µg/mL; A:0.002–32; V:0.002–32µg/mL; I: 0.002–32 µg/mL; F: 0.016–256 µg/mL; P: 0.002–32 µg/mL.

Medical treatment was considered successful when complete epithelial healing was seen with no fluorescein staining and infiltrate resolution to scar. Delayed healing was considered as epithelial healing with no fluorescein staining and infiltrate resolution, decrease of 20% in ulcer size, stromal infiltrate not healed, and requiring prolonged medical therapy. Failure of medical treatment was considered with no

ISSN (O): 2687-5365; ISSN (P): 2753-6556

epithelial healing, need for therapeutic keratoplasty/surgical intervention, perforation, and increase in infiltrate.

Collected data were statistically analyzed using the chi-square test, Fisher's exact test, Mann Whitney U test, and SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk. NY, USA) using ANOVA, chi-square test, and student's t-test. The significance level was considered at a p-value of <0.05.

RESULTS

The present longitudinal prospective study was aimed to the clinical response in refractory cases of fungal keratosis after topical application of 1% posaconazole therapy. The study assessed 140 eyes of refractory fungal keratitis where 70 were taken for PCZ (posaconazole) treatment for 1% posaconazole therapy and 70 for conventional antifungal therapy. Parameters assessed in the study were demographic data, treatment details, clinical photography, comprehensive slit lamp biomicroscopy, visual acuity, and ASCOT at recruitment and weekly for weeks 1, 2, 3, and 4 following treatment initiation. Clinical assessment was grade of keratitis severity, healing time, and healing response. Anti fungal susceptibility testing was also done.

It was seen that for assessing the visual acuity in two groups of study subjects, for controls, PL (perception of light) was seen in 40% (n=28) subjects at 0 week, HMCF (Hand movements close to the face) was seen in 40% (n=28) subjects at 0 week and 8.57% (n=6) subjects at 4 weeks, FCCF (finger counting close to face) was seen in 5.71% (n=4) subjects at 0 week and 20% (n=14) subjects at 4 weeks, and >FC 1m was seen in 71.43% (n=50) subjects at 4 weeks. In cases, PL was seen in 37.14% (n-26) subjects at 0 week, HMCF in 62.86% (n=4) subjects at 0 week and 14.28% (n=10) subjects at 4 weeks, FCCF in 2.8% (n=2) subjects at 0 and 22.85% (n=16) subjects at 4 weeks, and >FC 1m was seen in 62.855 (n=44) subjects at 4 weeks [Table 1].

The study results showed that for ulcer characteristics in study subjects, healing time was 27.11±5.6 days in PCZ and 26.39±4.79 days in conventional management group depicting statistically non-significant difference with p=0.58. Similar non-significant difference was seen for hypopyon, endothelial plaque, stromal infiltrate, and epithelial ulcers with p=0.08, 0.33, 0.44, and 0.58 respectively. For healing response in study subjects, TPK (therapeutic keratoplasty) was needed in 14.28% (n=10) subjects in PCZ and 20% (n=14) subjects in conventional management group showing statistically non-significant difference with p=0.52. Similar non-significant results were seen for delayed healing and healing in PCZ and conventional group with p=0.74 and 0.63 respectively [Table 2].

On assessing the antifungal susceptibility in study subjects, penicillin had susceptibility to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin) in 100%, 0, 90%, 80%, 10%, 100%, and 8% (n=4) subjects. 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].

In conventional treatment group, Rhizopus had sensitivity to P, F, I, V, A, and N in 90%, 0, 33%, 30%, 60%, 80%, and 2.85% (n=2) subjects respectively. Penicillin had sensitivity to P, F, I, V, A, and N in100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) subjects respectively. Altemaria had sensitivity to P, F, I, V, A, and N in 100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) subjects respectively. Cladosporium had sensitivity to P, F, I, V, A, and N in 96.6%, 66.2%, 66.6%, 66.6%, 80%, 90%, and 5.71% (n=4) subjects respectively. A. furigatus had sensitivity to P, F, I, V, and A in 100%, 10%, 100%, 96%, 91%, and 92% subjects respectively. A. niger had sensitivity to P, F, I, V, and A in 100%, 10%, 100%, 95%, 90%, and 33.4% subjects respectively. A. flavus had sensitivity to P, F, I, V, and A in 86.7%, 13.4%, 88.7%, 93.4%, 30%, and 63.4% subjects respectively. Fusarium had sensitivity to P, F, I, V, A, and N in 90%, 18.4%, 15.4%, 68.6%, 60%, 89.3%, and 42.85% (n=30) subjects respectively [Table 3].

Table 1: Visual acuity in two groups of study subjects

S. No	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
1	Controls	28 (40)	-	28 (40)	6 (8.57)	4 (5.71)	14 (20)	-	50 (71.43)
2	Cases	26 (37.14)	-	42 (62.86)	10 (14.28)	2 (2.8)	16 (22.85)	-	44 (62.85)

Table 2: Ulcer characteristics in study subjects

S. No	Ulcer characteristics	PCZ (n=70)	Conventional management (n=70)	p-value
1.	Healing time (days)			
a)	Total healing time	27.11±5.6	26.39±4.79	0.58

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b)	Hypopyon	16±4.53	17±5.55	0.08
c)	Endothelial plaque	16±3.68	19±3.38	0.33
d)	Stromal infiltrate	21.14±4.79	22.18±4.25	0.44
e)	Epithelial ulcer	27.11±5.6	26.39±4.79	0.58
2.	Healing response in study subjects n (%)			
a)	TPK (therapeutic keratoplasty)	10 (14.28)	14 (20)	0.52
b)	Delayed healing	6 (8.5)	4 (5.71)	0.74
c)	Healed	54 (77.14)	52 (74.28)	0.63

Table 3: Antifungal susceptibility in two groups of study subjects

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

DISCUSSION

The study results showed that for assessing the visual acuity in two groups of study subjects, for controls, PL (perception of light) was seen in 40% (n=28) subjects at 0 week, HMCF (Hand movements close to the face) was seen in 40% (n=28) subjects at 0 week and 8.57% (n=6) subjects at 4 weeks, FCCF (finger counting close to face) was seen in 5.71% (n=4) subjects at 0 week and 20% (n=14) subjects at 4 weeks, and >FC 1m was seen in 71.43% (n=50) subjects at 4 weeks. In cases, PL was seen in 37.14% (n-26) subjects at 0 week, HMCF in 62.86% (n=4) subjects at 0 week and 14.28% (n=10) subjects at 4 weeks, FCCF in 2.8% (n=2) subjects at 0 and 22.85% (n=16) subjects at 4 weeks, and >FC 1m was seen in 62.855 (n=44) subjects at 4 weeks. These data were comparable to the previous studies of Prajna NV et al,[6] in 2016 and Kredics L et al,[7] in 2015 where visual acuity results similar to the present study were also reported by the authors in their respective studies.

It was seen that for ulcer characteristics in study subjects, healing time was 27.11±5.6 days in PCZ and 26.39±4.79 days in conventional management group depicting statistically non-significant difference with p=0.58. Similar non-significant difference was seen for hypopyon, endothelial plaque, stromal infiltrate, and epithelial ulcers with p=0.08, 0.33, 0.44, and 0.58 respectively. For healing response in study subjects, TPK (therapeutic keratoplasty) was needed in 14.28% (n=10) subjects in PCZ and 20% (n=14) subjects in conventional management group showing statistically non-significant difference with p=0.52. Similar non-significant results were seen for delayed healing and healing in PCZ and conventional group with p=0.74 and 0.63 respectively. These results were consistent with the findings of Lalitha P et al,[8] in 2007 and Nayak N et al,[9] in 2011 where ulcer characteristics reported by the authors in their studies were comparable to the present study.

Concerning the assessment of the antifungal susceptibility in study subjects, penicillin had susceptibility to P (posaconazole), F (fluconazole), I (itraconazole), V (voriconazole), A (amphotericin), and N (natamycin) in 100%, 0, 90%, 80%, 10%, 100%, and 8% (n=4) subjects. 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. These findings were in agreement with the results of Castillo Castañeda A et al,[10] in 2020 and Gueudry J et al,[11] in 2020 where antifungal susceptibility in study subjects on 1% PCZ comparable to the present study were also reported by the authors in their studies.

It was also seen that on conventional treatment group, Rhizopus had sensitivity to P, F, I, V, A, and N in 90%, 0, 33%, 30%, 60%, 80%, and 2.85% (n=2) subjects respectively. Penicillin had sensitivity to P, F, I, V, A, and N in100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) subjects respectively.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Altemaria had sensitivity to P, F, I, V, A, and N in 100%, 10%, 80%, 90%, 40%, 100%, and 5.71% (n=4) subjects respectively. Cladosporium had sensitivity to P, F, I, V, A, and N in 96.6%, 66.2%, 66.6%, 66.6%, 80%, 90%, and 5.71% (n=4) subjects respectively. A. furigatus had sensitivity to P, F, I, V, and A in 100%, 10%, 100%, 96%, 91%, and 92% subjects respectively. A. niger had sensitivity to P, F, I, V, and A in 100%, 10%, 100%, 95%, 90%, and 33.4% subjects respectively. A. flavus had sensitivity to P, F, I, V, and A in 86.7%, 13.4%, 88.7%, 93.4%, 30%, and 63.4% subjects respectively. Fusarium had sensitivity to P, F, I, V, A, and N in 90%, 18.4%, 15.4%, 68.6%, 60%, 89.3%, and 42.85% (n=30) subjects respectively. These results were in line with the findings of Vanathi M et al,[12] in 2022 and Durgun ME et al,[13] in 2022 where antifungal susceptibility in subjects on conventional therapy reported by authors in their studies were comparable to the results of the present study.

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.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556