Int. J Med. Pharm. Res. (P-ISSN: 2958-3675 | E-ISSN: 2958-3683)
Available on: https://ijmpr.in/

International Journal
of Medical and Pharmaceutical Research

ORGINAL ARTICLE **OPEN ACCESS**

Topical versus Intrastromal Voriconazole for treatment of Recalcitrant fungal Corneal Ulcer: A Randomised Controlled Trial

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OPEN ACCESS

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Received: 26-06-2024
Accepted: 05-08-2024
Available online: 08-08-2024

A B S T R A C T

Purpose*:** To compare the safety and efficacy of intrastromalvoriconazole injection with topical voriconazole in management of fungal corneal ulcer not responding to conventional therapy.Patients and methods*:** A comparative and randomized study performed on patients with resistant fungal keratitis.Half of the patients (Group A) were given intrastromal injection in the dose of 0.1 ml (50 microgram/0.1ml) in each injection , Half of the patients (Group B) were given topical voriconazole eye drops (1%) once hourly. Healing of keratitis was considered as primary outcome measure.***Results*:** Each group included 35 eyes with resistant fungal keratitis. Complete healing of fungal keratitis was higher in group A (88.6%) than in group B (31.4%) and the difference was statistically significant (P<0.05). Duration of healing ranged between 2-4 weeks in group A and between 2-6 weeks in group B (P>0.05).***Conclusion*:** Voriconazole topically might be effective for treatment of resistant fungal keratitis. Adding intrastromal injection to topical drops could significantly raise the healing rate and hasten the resolution period without significant complications related to injection.

INTRODUCTION

Fungal keratitis can be defined as one of the mostly caused diseases of the eye that can often lead to complete or partial blindness. Among some of the most common reasons behind the occurrence of any kind of infection related to the vision is due to an injury. This can be a day to day injury as well, for example, trauma by plant material such as a branch or thorn can get into the eye, penetrate the safety layer and cause an infection. Fungal keratitis is rare in temperate countries but is a major cause of visual loss in tropical and developing countries.

An intrastromal injection of voriconazole (50 microgram/0.1 ml) was used around the affected area of the ulcer. Voriconazole is a triazole antifungal agent, structurally related to fluconazole but with a fluoropyrimidine group in place of triazolemoiety, similar to other triazole agents it inhibits the enzyme 14 alpha lanosteroldemethylase leading to lower level of ergosterol which is an essential component of fungal cell wall [1].

The aim of this study is to compare the safety and efficacy of topical versus intrastromal injection plus topical voriconazole for treatment of deep or resistant fungal corneal ulcer.

Patients and Methods:

Patients with fungal corneal pathology which were resistant to conventional therapy were identified and were being included in study after obtaining informed consent. Half of thepatients (Group A) were given intrastromal injection in the dose of 0.1 ml (50 microgram/0.1ml) in each injection with 1 ml tuberculin syringe at 3 to 4 sites in midstroma of junction of clear cornea and stromal infiltrates, divided equally around the lesion. Half of the patients (Group B) were given topical voriconazole eye drops (1%) once hourly. Patients were followed up on Next day, Daily basis for 1 week and then twice weekly post treatment. . The inclusion criteria were Presence of fungal corneal ulcer at the time of presentation (corneal epithelial defect with stromal infiltration) and Patients presented with fungal corneal ulcers which

were resistant to other antifungal therapy for at least 2 weeks. The exclusion criteria included Patients with perforated corneal ulcer, systemic diseases like uncontrolled diabetes mellitus, immunocompromised patients and patients with endophthalmitis.

Every patient underwent a thorough medical history, covering risk factors for fungal keratitis such as previous trauma, contact lens wear, chronic topical steroid use, and surgical procedure history. A thorough examination of the eyes was done, paying particular attention to the cornea and anterior portion. In order to rule out endophthalmitis, B scan ultrasonography was performed if the posterior portion could not be seen.

Corneal scraping from base and edge of ulcer was done, under topical anaesthesia. The scraped material was subjected to direct smear and Sabouraud dextrose agar culture.

Preparation and injection of intrastromalvoriconazole:

Voriconazole powder was divided into Epindorf tubes under fully aseptic circumstances. Each tube held 2 mg of dry lyophilized powder, which was then reconstituted in the Micro Safety Cabinet laminar flow apparatus with 4 ml of lactated Ringer solution to yield a 500 µg/ml (50 µg/0.1 ml) concentration. Each syringe held 0.5 ml of the reconstituted solution, which was maintained under strict aseptic conditions. The reconstituted solution was put into one-milliliter tuberculin syringes fitted with 27-gauge needles.

Under an operating microscope, the preloaded voriconazole was injected into the cornea following topical and local anesthetic. The needle was introduced obliquely, bevel down, from the clean, uninvolved cornea to just flush the ulcer at the mid-stromal level (the level desired for drug deposit). Following the injection of the medication, the area covered was measured using the cornea's moisture level as a reference.For every intrastromal injection, a total of 0.05 to 0.1 ml of medication was injected [2].

Preparation of topical voriconazole:

The glass vial containing the 200 mg lyophilized powder is filled with 19 ml of sterile distilled water for injectable purposes. This creates a 20 ml aqueous voriconazole solution that has a concentration of 10 mg/ml (1%). Voriconazole eye drops (1%) were aseptically prepared in a laminar flow device (Micro-Safety Cabinet). Voriconazole eye drops that had been reconstituted were aseptically injected into sterile droppers that were stored in an entirely aseptic environment. Hourly doses of 1% voriconazole eye drops were administered, and the treatment was continued for at least two weeks following the infection's full remission. Following the start of treatment, follow-up was conducted twice a week for the first week.

RESULTS

The studyincluded70eyeswithdeepand/orresistantfungalkeratitis,thatwererandomlydistributedbetweenthetwogroupsaccording to their order of presentation: group (A) included 35 eyeswhichreceivedintrastromalinjectionofvoriconazoleplustopicalvoriconazole eye drops and group (B) included 35 eyes which receivedtopical voriconazole eye drops alone.

Table 1: Shows distribution of study subjects according to age

	N	Minimum	Maximum	Mean	Std. Deviation	t-test	p-value
Group A	35	24.00	66.00	41.9714	10.22824	2.772	0.055*
Group B	35	23.00	67.00	45.4857	10.89353		

Table no 1shows distribution of study subjects according to age. Maximum cases in Group A (37.14%) were aged 31-40yrs with mean age being 41.97±10.23yrs; whereas maximum cases in Group B (42.86%) were aged 41-50yrs of age with mean age being 45.49±10.89yrs

Table 2: Shows distribution of study subjects according to history of injury

H/0 injury	Group A		Group B	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Foreign body	4	11.4	3	8.6
Vegetative matter	22	62.9	24	68.6
Wooden stick	8	22.9	8	22.9
With thorn	1	2.9	0	0
Total	35	100.0	35	100.0
Chi square	2.355			
p-value	0.088*			

Table no 2shows distribution of study subjects according to history of injury. Maximum cases in Group A and B (62.9% and 68.6% respectively) showed injury from vegetative matter, followed by (22.9%) with wooden stick, and foreign body. Chi square statistical analysis revealed an insignificant difference (p-value>0.05) between both the groups in relation to history of injury.

Table 3: Shows distribution of study subjects according to size of ulcer (mm)

Size of ulcer (mm^2)	Group A		Group B	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
<10	8	22.85714	2.0	5.714286
10 to 20	23	65.71429	11.0	31.42857
>20	4	11.42857	22.0	62.85714
Total	35	100	35.0	100
Chi square	3.492			
p-value	0.003*			

Table no 3 shows distribution of study subjects according to size of ulcer (mm). Maximum cases in Group A (28.6%) showed 4*4 sq mm size of lesion, whereas in Group Bmaximum (20%) cases showed a larger 5*5 sq mm size of lesion. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the groups in relation to size of ulcer.

Table 4: Shows distribution of study subjects according to depth of ulcer

Depth of ulcer	Group A		Group B	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
$1/3^{rd}$	21	60.0	3	8.6
$2/3^{rd}$	14	40.0	32	91.4
Total	35	100.0	35	100.0
Chi square	1.778			
p-value	0.0289*			

Table no 4shows distribution of study subjects according to depth of ulcer. Maximum cases in Group A (60%) showed $1/3^{rd}$ depth of ulcer, whereas in Group Bmaximum (91.4%) cases showed depth of ulcer upto 2/3rd. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the groups in relation to depth of ulcer.

Table 5: Shows distribution of study subjects according to hypopyon

Hypopyon	Group A		Group B	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
-	16	45.7	11	31.4
+	19	54.3	24	68.6
Total	35	100.0	35	100.0
Chi square	2.220			
p-value	0.045*			

Table no 5shows distribution of study subjects according to hypopyon. Maximum cases in Group A and Group B (54.3% and 68.6% respectively) showed positive hypopyon. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the groups in relation to hypopyon.

Table 6: Shows distribution of study subjects according to size of ulcer (mm) after 10-14days

Size of ulcer	Group A		Group B	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
<10	28	80	3.0	8.571429
10 to 20	7	20	6.0	17.14286
>20	0	0	26.0	74.28571
Total	35	100	35.0	100
Chi square	3.667			
p-value	0.025*			

Table no 6shows distribution of study subjects according to size of ulcer (mm) after 10-14days. Maximum cases in Group A (31.4%) showed 3*2 sq mm size of ulcer, whereas in Group Bmaximum (17.1%) cases showed a larger 7*6

sq mm size of lesion. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the groups in relation to size of ulcer after 10-14days.

Table 7: Shows distribution of study subjects according to response

Response	Group A		Group B	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Good healed	31	88.6	11	31.4
Not healed	4	11.4	24	68.6
Total	35	100.0	35	100.0
Chi square	2.889			
p-value	0.002*			

Table no 7shows distribution of study subjects according to response. Maximum cases in Group A (88.6%) showed good healing, whereas in Group B maximum (68.6%) cases showed no healing. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the groups in relation to response.

DISCUSSION

Fungal infections typically result in fungal endophthalmitis, progressive corneal ectasia. The corneal stroma injection technique was used by a number of studies to improve the local drug concentration in the corneal lesion and to address the problem of antifungal drugs' limited penetrability into the corneal stroma [3, 4]. There is conflicting evidence about the effectiveness of intrastromalvoriconazole injection in treating fungal keratitis, despite research suggesting that it may raise drug concentrations in the corneal stroma. These variations could be linked to the different injection techniques employed in different investigations, which led to different drug concentrations and distributions in the corneal stroma. At the same time, some studies have suggested that intrastromal injections were dangerous and increased the risk of corneal perforation [5].Thus the present study was conducted to assess the safety and efficacy of topical voriconazole against intrastromal injection for treating fungal corneal ulcers that have resisted conventional treatment because very few studies have been done on comparison basis.

Maximum cases in Group A (37.14%) were aged 31-40yrs with mean age being 41.97±10.23yrs; whereas maximum cases in Group B (42.86%) were aged 41-50yrs of age with mean age being 45.49±10.89yrs, with insignificant difference (p-value>0.05) statistically between both the groups in relation to age. Maximum cases in Group A and B were males (80% and 71.4% respectively), showing male predominance, with an insignificant difference (p-value>0.05) between both the groups statistically. Most of the subjects were farmers, showing that farmers were more prone to fungal infections of eye. Similar to our study, evaluated the role of intrastromal injection of voriconazole for managing the deep fungal keratitis cases which are not responding to the conventional management [6]. In their study, male predominance was observed, with age ranging from 40 to 65 years, mean being 52.75 years. In accordance with our study, found that maximum cases suffering with fungal infections of eye were engaged in agriculture [7]. Maximum cases in Group A and B (62.9% and 68.6% respectively) showed injury from vegetative matter, followed by (22.9%) with wooden stick, and foreign body, revealing an insignificant difference (p-value>0.05) between both the groups in relation to history of injury.

Affectivity of both intrastromal and topical voriconazole was also compared by assessing change in the size of infiltrate or scar before and after starting the treatment in both the groups. In our study, maximum cases in Group A (28.6%) showed 4*4 sq mm size of lesion, whereas in Group Bmaximum (20%) cases showed a larger 5*5 sq mm size of lesion. After subjecting patients to respective treatment modalities in both the groups, it was observed that maximum cases in Group A (31.4%) showed 3*2 sq mm size of ulcer, whereas in Group Bmaximum (17.1%) cases showed a larger 7*6 sq mm size of lesion. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the groups in relation to size of ulcer after 10-14days. The results revealed a considerable decrease in the size of lesion in cases managed using intrastromalvoriconazole as compared to cases which were managed using topical voriconazole. In a study conducted bythe size of ulcers ranged from 2 to 5 mm, with the mean depth of $315.43 \pm 57.72\ \mu$m [10]. Use of intrastromalvoriconazole injection together with topical voriconazole helps in reducing the size of infiltration effectively and also controlled the spread of infection in patients suffering with Fusarium keratitis [8]. After the targeted delivery of voriconazole through the intrastromal injection, a fast decline was observed in the corneal infiltration size and within 6 weeks of time, a complete ulcer resolution was seen [9].

In our study, maximum cases in Group A and Group B (54.3% and 68.6% respectively) showed positive hypopyon, showing a significant difference (p-value<0.05) between both the groups in relation to hypopyon statistically. Similar to our study, found that the mean size of infiltrate was 35. 88 mm^2 with presence ofhypopyonin 75% patients.In our study, maximum cases in Group A (88.6%) showed good healing, whereas in Group Bmaximum (68.6%) cases showed no healing. Chi square statistical analysis revealed a significant difference (p-value<0.05) between both the

groups in relation to response. Thus, we observed a significant positive response in patients being treated using intrastromal injection of voriconazole, as compared to topical voriconazole.

CONCLUSION

Deep or resistant fungal keratitis may respond well to voriconazole eye drops or intrastromal injection. When combined with topical drops, intrastromal injection has the potential to accelerate the healing process and reduce the amount of time needed for resolution while posing no serious injection-related risks. Due to the shortened hospital stay and quicker patient return to normal activities, this is more cost-effective.

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