Corneal intrastromal injection versus topical Voriconazole for management of fungal corneal ulcers

Hany Mahmoud Abdel Hamid, MBBCh[1], Usama Ali Mohammed, MD[1], Ali M Ismail, MD[1].

Affiliations and Addresses

[1]*The Department of Ophthalmology, Sohag Faculty of Medicine, Sohag University, 82524 Sohag, Egypt*

Abstract

PURPOSE: To evaluate the efficacy of intrastromal in comparison to topical Voriconazole in the management of fungal corneal ulcers.

DESIGN: prospective interventional comparative study.

PATIENTS& METHODS : Forty eyes of 40 patients who suffered from uncomplicated fungal corneal ulcer were enrolled in this study, they were subjected to the following : Full history taking, visual acuity (VA), slit lamp biomicroscopy , ultrasonography (to assess the posterior segment),corneal scraping for potassium hydroxide (KOH) test and culture to confirm fungal infection and identify species(if possible). Patients were divided in two groups: Group 1: 20 eyes received one intrastromal injection with Voriconazole (50 microgram /0.1 ml) at the junction of clear cornea and infiltrates, using a 30-gauge needle in five sites to form a barrage around the ulcer.

Group 2: The other 20 eyes received topical antifungal (Voriconazole eye drops (E.D) 1%). Both groups received topical Moxifloxacin hydrochloride 0.5% E.D four times a day and 1% Isopto-atropine E.D twice a day. Treatment has been started as soon as the (KOH) test is positive and followed for at least 2 months

RESULTS:

Both groups were matched regarding the mean baseline BCVA (0.048±0.057 and 0.12±0.111) for group 1 and group 2 respectively (*P*=0.115).

In Both groups, the BCVA after intrastromal or topical Voriconazole improved significantly than the pre-treatment one.

When the mean post-treatment BCVA was compared between both groups, there was a significantly higher BCVA in group 1 than in group 2 (*P*=0.038). In group 1, complete healing was obtained in 17 eyes (85%) versus 6 eyes only in group 2 (30%) which also was a statistically significant difference between both groups (*P*=0.000). The mean resolution time did not vary significantly between both groups, it was 20.4 ± 3days for group 1 versus 26.4±3.50 days in group 2, *P*=0.13. Complication rate was higher for group 2 of topical treatment (25%) than for group 1(10%) but did not reach a statistically significant level (*P*=0.106).

CONCLUSION: Intrastromal injection is more effective in the management of fungal corneal ulcers than topical Voriconazole with less complications and a higher success rate and may be used as an initial line of therapy for fungal corneal ulcers.

Introduction:

Fungal keratitis accounts for nearly 50% of all cases of infectious keratitis in developing countries and has a poor prognosis compared with bacterial keratitis.[1, 2] Currently available topical antifungal drugs have limitations such as poor penetration into the eye, limited spectrum of activity and surface toxicity.[3-5] Surgical intervention in the form of therapeutic Keratoplasty is required more often in cases of fungal keratitis, compared with bacterial keratitis, indicating a poor response to treatment with antifungal agents.[2,6]

A less invasive surgical modality of use of intrastromal Amphotericin B and Voriconazole for cases of deep-seated fungal keratitis, non-responsive to topical and oral antifungal agents have been described in anecdotal reports.[7-9]

Voriconazole, a more recent azole antifungal drug, is available commercially for systemic administration in the form of oral and intravenous formulations. It has an excellent broad spectrum antifungal activity and is active against species that are known to be resistant to the other antifungal agents commonly used in fungal keratitis.[10]

Voriconazole is increasingly being used topically as eye drops. Topical Voriconazole has demonstrated good penetration into the different parts of the eye,[11,12] with sufficient concentrations achieved to cover a wide range of keratitis-causative fungi.[10] Few recent papers showed that Voriconazole is more effective when injected intrastromally. [8] So in our study we aim to compare intrastromal injection versus topical Voriconazole in the management of fungal corneal ulcers.

Herein, we report the results of using intrastromal Voriconazole as an initial line of therapy for 20 eyes with fungal keratitis and compare them with other 20 eyes received topical Voriconazole.

Patients and methods: Forty eyes of 40 patients with microbiologically proven fungal corneal ulcer were enrolled in this prospective comparative study from the outpatient ophthalmology clinic of Sohag University Hospital from January 1st to December 31st 2011. The study was conducted in accordance with the rules of the scientific ethical committee of the faculty. Informed consent was obtained from all subjects. The diagnosis of fungal infection was made on the basis of clinical evaluation, positive smear and/or cultures of the fungus.

Inclusion criteria

Patients with uncomplicated microbial keratitis and proven presence of fungal organism on smear and/or culture.

Exclusion criteria

Cases that had some involvement of adjacent sclera, impending or frank corneal perforation, presence of descemetocele and concomitant endophthalmitis were excluded from the study.

At the initial presentation, each patient underwent a detailed evaluation that included clinical history, recording of visual acuity and slit-lamp biomicroscopy. Corneal scrapings were obtained under topical anaesthesia

(0.4% Benoxinate hydrochloride) and were sent for microbiological investigation including a potassium hydroxide (KOH) wet-mount preparation, Gram smear and cultures on Sabouraud dextrose agar to confirm diagnosis. The diagnosis was made on the basis of clinical evaluation ,positive smear and/or cultures. Antifungal therapy was started as soon as fungus was identified by KOH wet-mount preparation with Moxifloxacin hydrochloride eye-drops (0.5%) four times a day and topical atropine two times a day. According to the type of therapy started with; the patients were divided into two groups:

Group 1: Randomly 20 eyes received intrastromal Voriconazole solution 50 micrograms/0.1 ml circumferentially around the fungal ulcer in a single dose.

Group 2: The other 20 eyes received topical antifungal (Voriconazole eye drops 1% every 2 hours) for four weeks.

Follow-up:

Follow-up continued for two months, the first visit was 2 days after start of treatment and repeated each other day for 2 weeks then weakly regarding:

-Size of the ulcer.

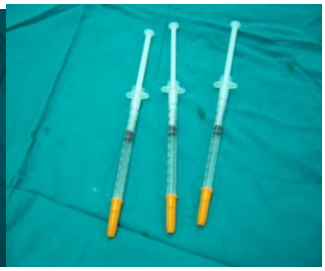
-Scar formation.

-Development of complications (perforation, endophthalmitis,…etc.)

The ulcer was defined as not improved if there was no change in the size of the ulcer or the infiltrates, and defined as worsened if there was an increase in size or depth of ulcer/infiltrate by 20% or perforation. All patients had deep-seated corneal infiltrates with or without hypopyon. The depth of corneal involvement in all these cases extended up to or deeper than midstromal level.

METHOD OF INTRASTROMAL INJECTION:

Voriconazole (VFEND) is available as 200 mg of white lyophilized powder in a glass vial (figure 1). The powder was reconstituted with 19 ml of lactated Ringer solution (LR) to obtain 20 ml of clear concentrate containing 10 mg/ml of Voriconazole. A 1-ml of this solution was further diluted with 20 ml of LR to a concentration of 0.5 mg/ml (50 microgram/0.1 ml). The reconstituted solution was loaded in a 1-ml tuberculin syringe with a 30-gauge needle (figure 1, 2).



(Figure 1) **(Figure 2)**

After administration of peribulbar anesthesia, the patient was shifted to the operating table. Under full aseptic Conditions, the preloaded drug was administered under Operating microscope. With the bevel down, the needle was inserted obliquely from the uninvolved, clear cornea to reach just flush to the ulcer at the mid-stromal level (as the intended level for drug deposit) in each case. The drug then was injected and the amount of hydration of the cornea was used as a guide to assess the area covered. Once the desired amount of hydration was achieved, the plunger was withdrawn slightly to ensure discontinuation of the capillary column and thus prevent back-leakage of the drug. Five divided doses were given around the ulcer to form a deposit

of the drug around the circumference of the lesion. The total amount of drug injected intrastromally ranged from 0.06 ml to 0.10 ml.(figure 3).

However, the topical 1% Voriconazole solution was stored under aseptic conditions at a temperature of 2-8ºC under refrigeration.[10] As per the Voriconazole package insert, the powder is reconstituted with 19 mL of water for injection to produce a 20 mL aqueous Voriconazole solution with a concentration of 10 mg/mL (1%).This Voriconazole solution is what is typically being used as eye drops.

Topical therapy was continued until 2 weeks after the resolution of the infection.

RESULTS:

The mean age of the patients in both groups was 56.586±15.13 years. There were 29 males and 11 females. The risk factors identified in these cases were trauma with vegetable matter (n=31), drugs abuse (topical corticosteroid drops or chronic topical antibiotics (n=6) and systemic disease (n=3), two cases were renal failure and one case was uncontrolled diabetes (Table 1).

No of patients	40 patients	Percentage%
Age	43 – 70 years	
Sex		
Male	29	72.50%
Female	11	27.50%
Risk factors		
plant trauma	31	77.50%
drugs abuse	6	15%
systemic disease	3	7.50%

Table 1: showing characters of patients at presentation

Both groups were matched regarding the mean baseline BCVA (0.048±0.057 and 0.12±0.111) for group 1 and group 2 respectively (*P*=0.115). In Both groups, the mean BCVA after intrastromal or topical Voriconazole improved significantly than the pre-treatment vision but improvement in group 1 was highly significant (*P*=0.000), whereas improvement in group 2 was just significant (*P*=0.05).

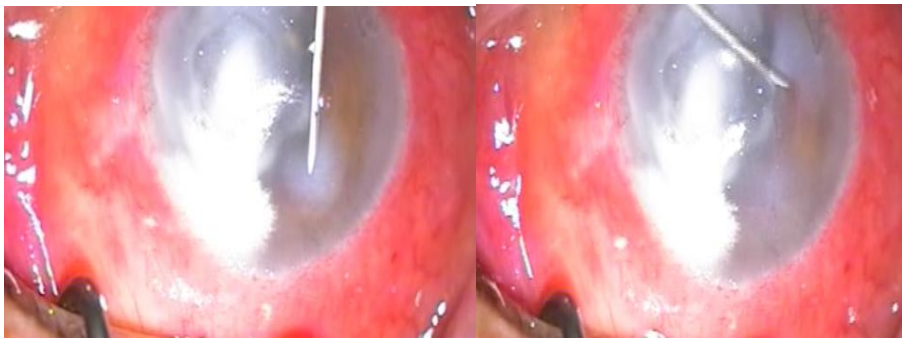
When compared between both groups, the post-treatment BCVA was significantly higher in group 1 than in group 2 (Table 2).

Group	**Pre-treatment mean BCVA**	**Post-treatment mean BCVA**	***P*-value**
Group 1	**0.048±0.057**	**0.351±0.15**	**0.000***
Group 2	**0.12±0.111**	**0.194±0.20**	**0.05***
***P*-value**	**0.115**	**0.038***	

***P-value is statistically significant**

Table 2. Comparison between pre-and post-treatment BCVA in both groups

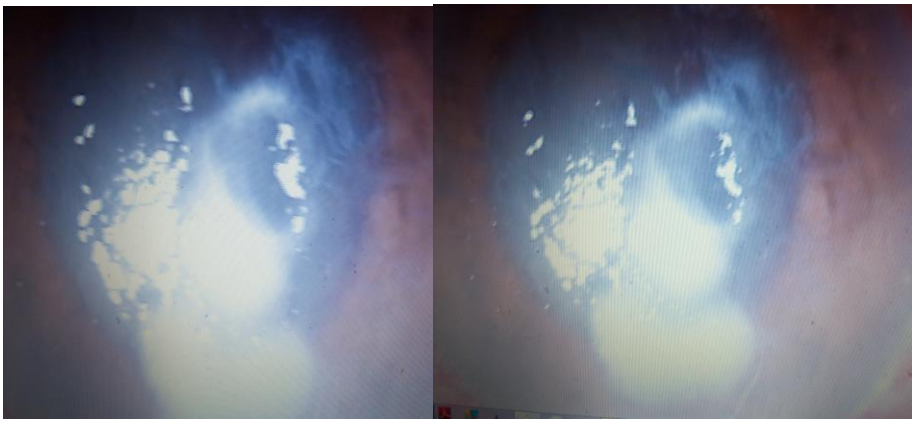
In group 1, complete healing was obtained in 17 eyes (85%) (figure 4) versus 6 eyes only in group 2 (30%) (figure 5) which also was a statistically significant difference between both groups (*P*=0.000) The mean resolution time was 20.4± 3days in group 1 compared to 26.4± 3.50 for group 2 without a significant difference (*P*=0.13).



(Figure3):showing method of intrastromal injection of voriconazole

Before intrastromal **two weeks after intrastromal**

(Figure 4) showing a case of fungal ulcer before and two weeks after intrastromal injection of Voriconazole.



(Figure5): showing a case of fungal ulcer before and two weeks after topical Voriconazole.

Complication rate was higher for group 2 of topical treatment (25%) than for group 1 (10%) but did not reach a statistically significant level (*P*=0.106). In group 1, two patients developed complications (one endophthalmitis and the other perforated ulcer). One patient was lost during the follow up. In group 2 of topical therapy, 5 eyes developed complications (3 perforated ulcers, 2 endophthalmitis), 3 eyes were lost during the follow up, 6 eyes were shifted to intrastromal injection after no improvement after 4 weeks. (Table 3)

	(Group1) with intrastromal injection of Voriconazole	**(Group 2) with topical Voriconazole**	**P-value**
No. Of eyes	20	20	
Success rate	85%	30%	0.000*
Complications	2 cases	5 cases	0.106

Table3: Comparison between intrastromal and topical Voriconazole.

No recurrence of keratitis were noted in either groups

DISCUSSION

Fungal keratitis can present as superficial keratitis, corneal abscess , and may be associated with hypopyon.[13] The commonly available antifungal agents are Amphotericin B, Natamycin, Fluconazole, Ketoconazole, 5-flucytosine, Itraconazole and voriconazole.[13] The fungistatic activity of Amphotericin B is limited against filamentous fungi, and its systemic use is associated with various side effects.[14] Natamycin has poor corneal penetration and precipitates on the corneal surface.[15] In vitro susceptibility data show that

Voriconazole has the best efficacy against pathogenic fungi compared with other agents.[16-18]

Voriconazole is a triazole antifungal agent and is a second-generation synthetic derivative of Fluconazole; it is effective against yeast and filamentous fungi. The primary mode of action of Voriconazole is the inhibition of cytochrome P-450-mediated 14-α-lanosterol demethylation, an essential step in fungal Ergosterol biosynthesis and the resulting Ergosterol depletion causes fungal cell wall destruction. It is well tolerated after oral administration; therapeutic aqueous and vitreous levels are achieved after administration of up to 200 mg twice a day.[8.12]

It is evident from previous studies that oral and topical antifungal agents have poor ocular penetration, thereby achieving suboptimal drug levels at the site of infection.[3-5, 15] hence, targeted drug delivery is required to achieve adequate drug levels at the site of infection.[19-22] In order to achieve adequate intracorneal concentration of antifungals, intrastromal injections of antifungals have been tried.[7-9]

In group 1 of this study, the drug was injected around the ulcer to form a drug deposit around the circumference of the lesion. This was done in such a manner that a centripetally directed progressive wave of fluid appeared to encompass the ulcer along each meridian. Circumferential injection ensured the formation of a barrage of intrastromal Voriconazole around the entire ulcer.

A statistically significant higher success rate with complete resolution of the ulcer was obtained in group 1 of intrastromal injection of Voriconazole (85%) than in group 2 of topical therapy (30%). These results are comparable to that reported by Prakash et al[8] where their study showed that 100 % success rate in three resistant cases of fungal ulcer.

Swapnil Madhukar et al reported a success rate of 66.6% after topical Voriconazole 1% in treatment of cases of severe fungal ulcer in combination with oral Voriconazole, the higher success rate in his series may be due to the additional effect of the oral dose.[24]

In this study, a significantly higher vision was obtained with intrastromally injected Voriconazole than topical one which means that it is more effective.

Also, we did not report any complications related to intrastromal Voriconazole injection which is also in agreement to that obtained by Prakash et al.[8]

Tu EY reported success with intrastromal Voriconazole in 3 cases of Alternaria infection, All patients presented with an indolent steroid-treated keratitis and a history of recent cataract surgery, agricultural trauma, or contact lens wear. None of the patients responded to natamycin, and 1 also failed to respond to topical and systemic voriconazole. Patients responded rapidly to either topical fluconazole 0.02% or a combination of intrastromal voriconazole and topical caspofungin 0.5%.[9]

Jain et al reported a good outcome in a case of fungal infection of the Phacoemulsification site tunnel with intrastromal voriconazole.[23]

This study has the largest series of patients with fungal keratitis treated primarily with intrastromal Voriconazole injection with a success rate of 85% at the end of 2 months follow-up. None of our patients developed any toxic effects with the drug after the injection. The results of this study regarding the significantly improved vision, higher success rate and lower complications with intrastromal Voriconazole may favorite this line of therapy as an initial line for management of fungal corneal ulcer. This will decrease the rate of complications during the treatment period than if other modality of therapy is used and also will decrease the rate of penetrating Keratoplasty as we will start the intrastromal injection early and will not wait until the ulcer become resistant with the resultant larger area of ulcer and infiltration which will heal with a large scar, but with early intervention scar may be smaller and may not necessitate Keratoplasty. Further studies and randomized controlled trials are recommended before this choice of treatment assumes a standard approach. The major advantage of this treatment modality is that it delivers the drug at the site of infection, achieving a high intracorneal concentration, which may not be possible with topical and systemic antifungal therapy.

In this study, we can conclude that, the safety of intrastromal injection is comparable to topical Voriconazole but with a more superior efficacy and less complications for the treatment of fungal ulcers which may favorite its use as an initial line of therapy.

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