

Original Article

INTRASTROMAL VORICONAZOLE AS A PRIMARY TREATMENT FOR
CLINICALLY DIAGNOSED FUNGAL KERATITIS IN CHILDREN.

Elkadim, M.^(*), Nassar, E., Saad, H. & Sharaf, A.
Ophthalmology dept., Faculty of Medicine, Tanta, Univ., Egypt.

*E-mail: mzekadem@gmail.com

Received: 27/12/2022

Accepted: 22/4/2023

Doi: 10.21608/ejco.2023.305200

Abstract

Purpose: to evaluate the outcome of voriconazole intrastromal injection as a primary treatment of clinically presumed fungal keratitis in pediatric age. **Methods:** Retrospective study performed in a tertiary care hospital and included 13 eyes of 13 children less than 18 years old presented with feathery corneal infiltration after trauma with organic material. Intrastromal voriconazole injection (200ug/0.1 ml) was done upon clinical diagnosis of fungal keratitis followed by topical antifungal eye drops. Reinjection was done after 48 hours of the 1st injection if no clinical improvement found. Outcome measures were the response to treatment, number of injections, duration of hospitalization and complications. **Results:** The mean age of children included was 7 ± 2.8 years (range: 4-12 years). Ten cases (77%) had clinical improvement after 24 hours of single intrastromal injection. One case improved after a second intrastromal injection of voriconazole and two cases had three injections before clinical improvement. Duration of hospitalization ranged from 2–7 days (2.5 ± 0.8 days). After 3 months of follow up all cases developed localized corneal opacity and none developed recurrence of infection. **Conclusions:** Early intracorneal injection of voriconazole is a safe and effective way to treat cases of fungal keratitis in children.

Keywords: Voriconazole, Intrastromal, Fungal keratitis

1. Introduction

Fungal keratitis is a sight-threatening condition that is common particularly in the agricultural countries [1]. Treatment with topical antifungal agents requires hourly instillation that may be difficult in uncooperative children [2]. Furthermore, unresponsiveness that may be encountered in deep fungal keratitis due to poor penetration of topical agents lead to delayed improvement in many cases [3]. Systemic administration of antifungals,

despite found to be effective in deep fungal keratitis, is complicated by concerns about systemic side effects, pediatric dose adjustment and longtime of treatment required [4]. Intrastromal injection of voriconazole was found to be an effective adjuvant treatment for fungal keratitis resistant to other treatment modalities [5-7]. A recent case report showed rapid recovery of aggressive fungal infection of the anterior segment of a child after

single intrastromal and intracameral injection of voriconazole [9]. The aim of this study was to evaluate the outcome of early intrastromal injection of vorico-

2. Methods

This was a retrospective study performed at tertiary care university hospital in the period from May 2021 to June 2022. The study followed the tenets of the 2013 Declaration of Helsinki and was approved by the local ethics committee of "Tanta University" Hospital (Tanta, Egypt) as 35201-1-22; informed consent was obtained from parents of all patients undergoing surgery. The study included 13 eyes of 13 children clinically diagnosed as fungal keratitis due to presence of corneal

2.1. Injection technique

Intrastromal injection was performed under general anesthesia using face mask in all cases. Before injection, superficial scraping of corneal infiltrates was performed using blade number 15 and plated on glass slide for microscopic examination, swabs for cultures and sensitivity were taken for both bacteria and fungi. Voriconazole (Vfend 200mg; Pfizer; USA) was prepared for intrastromal injection by dissolving 200 mg vial into 20 ml sterile water for injection, then diluting 1 ml (10mg) to 5 ml sterile water to get a concentration 200 ug/ 0.1ml. Injection of 0.2 ml (400 ug) intrastromal was done using 30 G needle. The needle was introduced in the healthy corneal stroma around the corneal infiltrate with bevel down. Injection was done at 2-3 sites till the stroma is hydrated. After injection, the treatment prescribed was topical voriconazole (Vfend; Pfizer; USA) (10mg/ml) every 2 hours, Natamycin 5% (Natamycin; Orchidia Pharma; Egypt) 5 times per day, cyclopentolate 1% (Swixolate; Chemipharma; Egypt) 3 times per day and tobramycin 0.3% eye drops (Tobrex;

nazole as a primary or first line treatment of clinically presumed fungal keratitis in pediatric age.

epithelial defect and infiltration with feathery edge after trauma caused by organic material. Inclusion criteria included newly diagnosed children (18 years old or younger) without previous medical treatment and size of corneal infiltration less than 5 mm in maximum diameter regardless of its depth. Patients older than eighteen years and children with other ocular disease, previous ocular surgery or received treatment before presentation were excluded.

Alcon; USA) 5 times per day. After injection, corneal infiltrate, epithelial defect and presence of hypopyon were assessed every 12 hours. If no improvement, a second intrastromal injection was done after 48 hours of the first injection. Children with clinical improvement in the form of quiet eye, decrease size of corneal infiltration, healing of epithelial defect and disappearance of hypopyon were discharged from the hospital and followed up weekly in the outpatient clinic. The regimen of treatment after discharge from the hospital included topical tobramycin 0.3% (Tobrex; Alcon; USA) and cyclopentolate 1% (Swixolate; Chemipharma; Egypt) eye drops 3 times per day for 10 days and topical antifungals: voriconazole (Vfend; Pfizer; USA) (10mg/ml) every 2 hours and Natamycin 5% (Natamycin; Orchidia Pharma; Egypt) 5 times per day continued one month after epithelial healing. Outcome measures were the response to treatment, number of injections, duration of hospitalization and complications.

3. Results

The mean age of patients included was 7 ± 2.8 years (range: 4- 12 years) 11 (85%) were males and 2 were females. The causative agent of corneal trauma was plant or wood stick in 9, nail in 2, food 1 and colored contact lens in 1 patient. All cases presented within 48 hours of ocular trauma. All causes had corneal epithelial defect and stromal infiltration with feathery edge, 1 case had partial thickness corneal wound sutured with 10-0 nylon before injection and 2 had hypopyon on presentation. Fungi were detected in the smears of 11 children. And cultures were positive for fungi in

all cases. Ten cases had clinical improvement after 24 hours of single intrastromal injection, however, one case had clinical improvement after a second intrastromal injection of voriconazole and two cases had three injections before clinical improvement, fig. (1 & 2). Cultures from the three cases with repeated intrastromal injections revealed filamentous fungi, tab. (1). Duration of hospitalization ranged from 2-7 days (3 ± 1.7 days). After 3 months of follow up all cases developed corneal opacity at the site of infiltration and none developed recurrence of infection.

Figure 1: Response to single intrastromal injection of voriconazole *Left* (pictures before injection), *Right* (pictures after 1 week of injection).

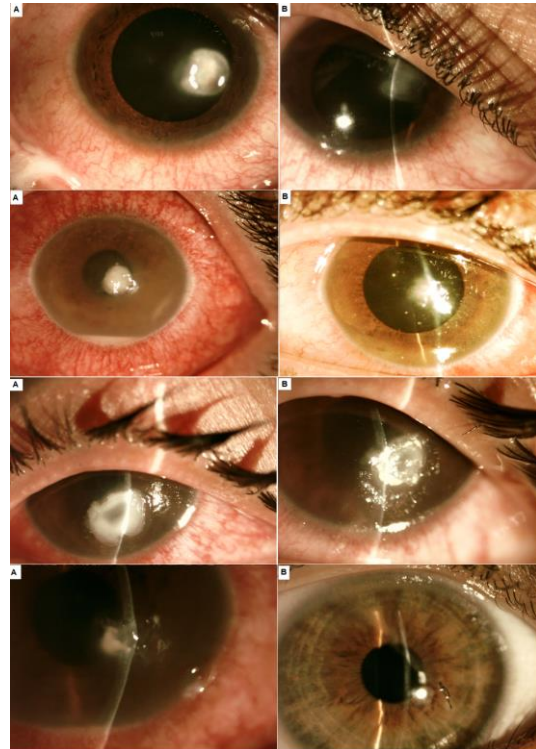


Figure 2: Improvement of corneal infiltration in a case required 3 intrastromal injections; *a.* on presentation, *b.* after 2 intrastromal injections, *c.* clinical improvement after 3rd injection, *d.* complete healing 2 weeks later.

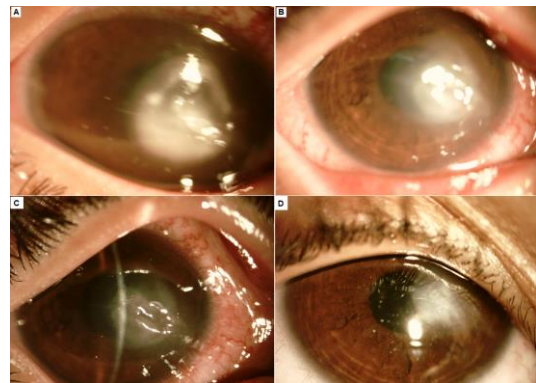


Table 1: Details of the studied cases

No	Age (Y)	Causative agent	Smear	Culture	Number of injections	Hospitalization (days)
1	5	plant stick	fungal	Filamentous	2	4
2	12	Contact lens	fungal	Yeast	1	2
3	4	wood	fungal	Yeast	1	2
4	7	plant stick	fungal	Filamentous	3	7
5	7	plant stick	Inflammatory cells	Yeast	1	3
6	4	nail	fungal	Yeast	1	2
7	10	plant stick	fungal	Filamentous	1	2
8	4	Food (bread)	fungal	Filamentous	3	6
9	8	nail	fungal	Yeast	1	2
10	6	plant stick	Inflammatory cells	Yeast	1	2
11	9	wood	fungal	Filamentous	1	2
12	5	plant stick	fungal	Yeast	1	2
13	11	plant stick	fungal	Yeast	1	3

4. Discussion

Fungal corneal infections are usually resistant and difficult to be treated. This is because fungi tend to penetrate deeply in the corneal stroma through a small epithelial defect causing deep keratitis and in some cases can progress to fungal endophthalmitis [9]. Cornea in pediatric age differs from adult cornea, being less stiff and having less compact corneal lamellae. This may facilitate rapid spread of fungal infection [10,11]. Furthermore, the large molecular weight of most anti-fungal agents results in poor penetration in the deep stroma [12]. Delayed response to topical or systemic medications may be associated with later larger corneal scar and poor visual outcome [13]. The condition in children is more complicated as they are more exposed to corneal trauma, less compliant with frequent medications and the risk of poor outcome due to amblyopia. In case of resistant fungal keratitis, therapeutic keratoplasty may be the last resort; however keratoplasty in children is usually associated with poor outcome [14]. Intrastromal injection of amphotericin is another option for fungal

keratitis, however, it was associated with deep corneal vascularization and toxicity [15]. Voriconazole has a broad spectrum that covers many strains of fungi and acanthamoeba and can be used topically and systemically [16]. Previous study showed significantly lower concentration of voriconazole after topical administration in comparison with combined topical and systemic administration [2]. Here comes the importance of voriconazole intrastromal injection to deliver the drug directly to the site where it should act. A recent study showed more rapid epithelial healing in a group of fungal keratitis patients treated with intrastromal injection of voriconazole in comparison to control group treated with conventional topical antifungal therapy with no significant difference in the final endothelial cell count between both groups [17]. The effective and safe concentration of voriconazole for intrastromal injection varied among studies from 50 to 10000 ug/ 0.1 ml. Studies showed that intrastromal injection of (50 µg/0.1 mL) voriconazole is effective against candida fungal keratitis

however; its effect against *Fusarium* species is inadequate [7] with treatment response similar to that of topical natamycin [18,19]. Another study showed resistance of *Fusarium* to intrastromal injection of 1000 ug/ 0.1 ml voriconazole [20]. Repeated intrastromal injection of 10000ug/0.1ml voriconazole combined with corneal debridement appears to be an effective treatment for *Fusarium* keratitis [21]. In animal study, intrastromal injection of voriconazole (5000 ug/0.1 ml) was associated with resolution of stromal keratitis and uveitis in all eyes [22]. As regard safety, Intracameral injection of voriconazole was found to be safe to rabbit corneal endothelial cells in a concentration up to 1000ug/0.1ml [23]. While a Transmission electron microscopy evaluation revealed definite necrotic changes in rabbit corneal endothelial cells after intrastromal injection of 100ug/ 0.1ml voriconazole [24]. In this study ten cases (77%) showed significant improvement after 1 intrastromal injection of voriconazole (200 ug/0.1 ml) with no clinically detected complications. The

difference between our study and previous studies is early intrastromal injection based on clinical diagnosis of fungal keratitis. In this study, intrastromal injection was the first line of treatment aiming to trap infections before they expand and invade more in the corneal stroma. Furthermore, causes proven to be infected with filamentous fungi eventually resolved despite required repeated injection. For a child rapid control of corneal fungal infection can be sight saving due to risk of rapid spread of infection, aggressive uveitis that can result in cyclitic membrane and atrophy of the bulb and at the best situation corneal opacification with deprivation amblyopia or high risk keratoplasty. Prevention of these catastrophic complications of fungal keratitis outweighs minimal risk of corneal toxicity from voriconazole intrastromal injection that was not clinically reported in previous studies even in extremely high concentrations. For this reason, we suggest that intrastromal voriconazole could be the first line of treatment for fungal keratitis in children.

5. Conclusion

Early intrastromal injection of voriconazole in pediatric fungal keratitis has excellent response, with rapid clinical improvement and could be a sight saving procedure.

Abbreviations

- *G*: gauge
- *Ug*: microgram
- *ML*: milli liter
- *Mg*: milligram.

Ethics approval and consent to participate

The study followed the tenets of the 2013 Declaration of Helsinki and was registered and approved by the local ethics committee of "Tanta University"

Hospital (Tanta, Egypt) with 35201, informed consent was obtained from parents of all children undergoing surgery

References

1. Acharya, Y., Acharya, B. & Karki, P. Fungal keratitis: Study of increasing trend and common determinants. *Nepal J. Epidemiol.* 2017; 7: 685-693

2. Thiel, M., Zinkernagel, A., Burhenne, J., et al. Voriconazole concentration in human aqueous humor and plasma during topical or combined topical and systemic administration for fungal keratitis. *Antimicrob Agents Chemother.* 2007; 51 (1): 239-244.
3. Li, J. Li, Z., Liang, Z., et al. Fabrication of a drug delivery system that enhances antifungal drug corneal penetration. *Drug Deliv.* 2018; 25 (1): 938-949.
4. Girois, S., Chapuis, F., Decullier, E., et al. Adverse effects of antifungal therapies in invasive fungal infections: Review and meta-analysis. *Eur. J. Clin. Microbiol. Infect. Dis.* 2005; 24 (2): 119-130.
5. Li, C., Pang, K., Du, L., Efficacy of voriconazole corneal intrastromal injection for the treatment of fungal keratitis. *J. Ophthalmol.* 2021; e559 7003.
6. Konar, P., Joshi, S., Mandhare, S., et al. Intrastromal voriconazole: An adjuvant approach for recalcitrant mycotic keratitis. *Indian J. Ophthalmol.* 2020; 68 (1): 35-38.
7. Kalaiselvi, G., Narayana, S., Krishnan, T., et al. Intrastromal voriconazole for deep recalcitrant fungal keratitis: A case series. *Br. J. Ophthalmol.* 2015; 99 (2): 195-198.
8. Albab, N. Oujidi, M., Belghamaidi, S., et al. Intrastromal injection of voriconazole as a therapeutic of fungal hypopyon: A case report. *Pan Afr. Med. J.* 2020; 21: 35-52
9. Zapp, D., Loos, D., Feucht, N., et al. Microbial keratitis-induced endophthalmitis: Incidence, symptoms, therapy, visual prognosis and outcomes. *BMC Ophthalmol.* 2018; 18 (1):112.
10. Mukhtar, S. & Ambati, B. Pediatric keratoconus: A review of the literature. *Int. Ophthalmol.* 2018; 38: 2257-2266.
11. Kotecha, A., Elsheikh, A., Roberts, C. et al. Corneal thickness- and age-related biomechanical properties of the cornea measured with the ocular response analyzer. *Invest. Ophthalmol. Vis. Sci.* 2006; 47: 5337-5347.
12. Kaur, I., Rana, C. & Singh, H. Development of effective ocular preparations of antifungal agents. *J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther.* 2008; 24: 481-493.
13. Haddad, R. & El-Mollayess, G. Combination of intracameral and intrastromal voriconazole in the treatment of recalcitrant Acremonium fungal keratitis. *Middle East Afr J Ophthalmol.* 2012; 19 (2): 265-268.
14. Zhang, Q. Zhao, M., Xu, M., et al. Outcomes of therapeutic keratoplasty for severe infectious keratitis in Chongqing, a 16-year experience. *Infect. Drug Resist.* 2019; 12: 2487-2493.
15. Saluja, G. Sharma, N., Agarwal, R., et al. Comparison of safety and efficacy of intrastromal injections of voriconazole, amphotericin B and natamycin in cases of recalcitrant fungal Keratitis: A randomized controlled trial. *Clin. Ophthalmol. Auckl. NZ.* 2021; 15: 2437-2446.
16. Raghavan, A., Nair, A., Venkatapathy, N., et al. Voriconazole in the successful management of a case of Acanthamoeba-Cladosporium keratitis. *Am. J. Ophthalmol. Case Rep.* 2021; 22; doi: 10.1016/j.ajoc.2021.101107.
17. Li, C., Pang, K., Du, L., et al. Efficacy of voriconazole corneal Intrastromal injection for the treatment of Fungal keratitis. *J. Ophthalmol.* 2021; doi: 10.1155/2021/5597003.
18. Edwar, L., Janna, Y., Rozaliyani, A., et al. Therapeutic response time of topical voriconazole 1% and intrastromal voriconazole 0.05% versus topical natamycin 5% monotherapy in Fusarium keratitis in rabbit. *Mycoses.* 2020; 63: 1128-1132.
19. Nejabat, M. Yaqubi, N., Khosravi, A., et al. Therapeutic effect of intrastromal voriconazole, topical voriconazole, and topical Natamycin on fusarium keratitis in Rabbit. *J. Ophthalmol.* 2016; doi: 10.1155/2016/ 8692830

20. Niki, M., Eguchi, H., Hayashi, Y., et al. Ineffectiveness of intrastromal voriconazole for filamentous fungal keratitis. *Clin. Ophthalmol. Auckl. NZ.* 2014; 8: 1075-1079.
21. Guber, I., Bergin, C. & Majo, F. Repeated intrastromal injections of voriconazole in Combination with Corneal debridement for recalcitrant fungal keratitis - a case series. *Klin. Monatsbl. Augenheilkd.* 2016; 233: 369-372.
22. Smith, K., Pucket, J. & Gilmour, M. Treatment of six cases of equine corneal stromal abscessation with intracorneal injection of 5% voriconazole solution. *Vet. Ophthalmol.* 2014; 17 (Suppl 1): 179-185.
23. Han, S., Yang, H., Hyon, J., et al. Toxicity of voriconazole on corneal endothelial cells in an animal model. *Br. J. Ophthalmol.* 2012; 96: 905-908
24. Park, C., Lee, H. & Chung, S. Toxicity of intrastromal voriconazole injection on corneal endothelium in rabbits. *Cornea.* 2014; 33: 928-934.