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Investigating the Effectiveness of Intrastromal Fluconazole Injection for Treating Fungal Keratitis; An Interventional Study

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Abstract:

Objective: To determine the effectiveness of Fluconazole injection in the management of fungal keratitis in patients attending a tertiary eye care hospital Sindh, Pakistan.

Methods: This was an interventional and prospective study with a non-probability convenience sampling method. It was carried out in the Ophthalmology department of Ghulam Muhammad Mahar Medical College (GMMMC) Sukkur, Sindh-Pakistan. The time duration was from January 2023 to January 2024. Ethical approval was taken from the Institutional Review Board (IRB) before the initiation of the study. Sample size drawn was 76. Inclusion criteria were patients diagnosed with fungal keratitis based on microbiological findings, corneal infiltration area should be < 10mm in diameter, history of vegetative trauma, satellite lesions on the cornea, corneal stoma and irrespective of age and gender. Exclusion criteria were other types of keratitis, perforation in the cornea, any stage of endophthalmitis, mature cataract,ocular diseases in combination, involvement of sclera, corneal transplantation and fungal infection overspreading stroma and anterior chamber.

Results: A total of 76 participants were included in this study. The mean age was 53.25±10.56 with range of 30-70 years. Mean duration of vegetative trauma at time of presentation was 10.05±4.34 days. There were 27 (35.53%) male and 49 (64.47%) female. There were 54 (71.05%) patients from rural side.Visual acuity status at the last follow-up of the third month showed improvement in visual acuity was seen in 63 (82.89%) respondents, vision remained stable in 11 (14.47%) however 2 (2.63%) had worsened their vision after intervention. Success rate was found to be 74 (97.36%) patients.

Conclusion: Fluconazole injection observed to be most effective drug to treat fungal keratitis mostly in vegetative trauma.

Keywords: Vegetative Trauma, Keratitis, Fungal Infection, Fluconazole

Introduction

Fungal keratitis treatment is a challenge for ophthalmologists and it is also a sight-threatening corneal infection .[1] Despite medical science advancement treatment of fungal keratitis is difficult. There are lots of antifungal agents but Fluconazole has played a very important role in the treatment of fungal keratitis. It is effective against multiple fungal pathogens. The use of intrastromal Fluconazole injection in the past few years has given breakthroughs in the treatment of fungal keratitis .[2]

Signs of Fungal keratitis are corneal inflammation and ulceration and it may lead to vision loss also, but the primary cause is usually by filamentous fungi such as Fusarium and Aspergillus. The incidence of fungal keratitis usually depends upon the agricultural practices, trauma and climatic conditions prone to fungal growth .[3] The prevalence rate is higher in the tropical and subtropical regions. [4] Risk increases for agricultural workers [5], contact lens wearers, [6] individuals with corneal trauma, or pre-existing ocular surface diseases. Delayed or wrong diagnosis may result in mismanagement of the disease that may result in corneal perforation, endophthalmitis, and irreversible visual impairment .[7]

Sometimes clinical signs and symptoms of fungal keratitis are mixed up with bacterial or viral keratitis which may mislead the diagnosis .[8] Conventional treatments like topical and systemic antifungal medications, corneal debridement, and in some cases, therapeutic keratoplasty are less efficient, need prolonged treatment duration, frequent medication instillation, and have a high risk of systemic side effects.

Fluconazole is a triazole antifungal agent, which is effective against multiple fungal agents like yeast, molds, and filamentous fungi. It has excellent corneal penetration and prolonged tissue retention ability, which makes it an attractive and effective treatment option as compared to conventional antifungal agents like natamycin and amphotericin B because of these characteristics Fluconazole has attained a cornerstone position in the management of fungal keratitis .[9]

Conventionally Fluconazole was administered topically but this route had some drawbacks like poor ocular bioavailability, patient compliance issues, and the need for frequent dosing. The biggest advantage of intrastromal Fluconazole injection is its application directly into the corneal stroma, which provides high intraocular concentration and lowers the risk of systemic side effects .[10] Moreover, this antifungal agent route of application aims to optimize therapeutic outcomes, accelerate corneal healing and decrease the risk of drug-related adverse effects .[11]

The rationale for Investigating Intrastromal Fluconazole Injection is very little research work has been done to evaluate the clinical evidence supporting the efficacy and safety in the management of fungal keratitis. Mostly the literature found is based on case studies, retrospective studies, and small-scale clinical trials with heterogeneous methodologies and inconsistent outcomes. There is a lack of standardized intrastromal Fluconazole injection treatment technique which makes it difficult to explain the therapeutic role of intrastromal Fluconazole injection in fungal keratitis but this study will help to fill this gap. The objective of this study is to determine the effectiveness of Fluconazole injection in the management of fungal keratitis.

Material and Methods

This was an interventional and prospective study with a non-probability convenience sampling method. It was carried out in the Ophthalmology department of Ghulam Muhammad Mahar Medical College (GMMMC) Sukkur, Sindh-Pakistan. The time duration was from January 2023 to January 2024. Ethical approval was taken from the Institutional Review Board (IRB) before the initiation of the study. The sample size was calculated from the online software openepi.com by taking 95% confidence interval and 5% margin of error.The prevalence of fungal keratitis in Pakistan was taken as 28.1% from a reference study done by Rizwan A et al, 2021.[12] The Sample size drawn from software was 76. A written informed consent was taken from each respondent. Inclusion criteria were patients diagnosed with fungal keratitis

based on microbiological findings, corneal infiltration area should be < 10mm in diameter, history of vegetative trauma, satellite lesions on the cornea, corneal stoma, and irrespective of age and gender. Exclusion criteria were other types of keratitis, perforation in the cornea, any stage of endophthalmitis, mature cataract,ocular diseases in combination, involvement of sclera, corneal transplantation and fungal infection overspreading stroma and anterior chamber.

About Injection and Follow-up criteria: Fluconazole is an antifungal injection of 2 mg/ml drug. All patients were given intrastromal injections. The dose was apporoximatlity 2mg/ml at 3 to 4 sites, in divided doses, in clear cornea around the lesion. It produced hydration of corneal stroma around the lesion.One ml syringe with a 7 gauge needle was used for injection, with the needle bevel downwards in corneal stroma. It was given on first, 4th,and 8th day of the presentation. Moderate to severe pain was a commoncomplaint by all patients which was treated by oral NSAIDS in all patients at the time of injection. Intrastromal injection was combined with topical anti fungal, Fluconazole eye drops 2mg/ml andantibiotic eye drops, Moxifloxacin 0.5% for 4 weeks. Patients were followed up on days two, five,nine, three weeks,and 3 months post-treatment. Best corrected visualacuity was noted at each visit.The patient was asked abou tpain and a slit lamp examination was done to note the size of the lesion, resolution of hypopyon, and epithelization of the defect.

Data collection procedure: The data was collected from the OPD following parameters related to demographics and clinical examination noticed on Proforma. After meeting inclusion criteria patients were given 2% Fluconazole injection by using 2mg/ml injectable topical solution. For corneal melting different drops as topical lubricant and Fluorometholone were added in selective patients.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 25.0. All continuous variables are presented as mean standard deviation. Categorical variables are presented as frequencies and percentages. To see the significance of follow-up Chi-square test was applied. A P-value < 0.05 is considered as statistically significant.

Results

A total of76 participants were included in this study. The mean age was 53.25±10.56 with range of 30-70 years. Mean duration of vegetative trauma at time of presentation was 10.05±4.34 days. There were 27 (35.53%) male and 49 (64.47%) female. There were 22 (28.5%)Urban residence observed while 54 (71.05%) from rural side and it was common area. (Table 1)

Demographic Characteristics of respondents:

	Mean± Standard Deviation	**Range**
Age (years)	53.25±10.56	30-70
duration of vegetative Trauma (days)	10.05±4.34	05-14
	Frequency (n=76)	Percent
Gender, n(%)		
Male	27	35.53
Female	49	64.47
Residencen(%)		
RURAL	54	71.05
Urban	22	28.95

Clinical features were observed as patients received with multiple symtoms i.e. eye pain and blurred vision were seen among all 76(100%) participants and eye redness was observed in 70 (92.11%). Signs were also

observed, corneal opacity was seen in 55(72.37%) respondents, corneal vascularization was observed in 32 (42.11%), ciliary congestion and blepharospasm were found in 76 (100%) participants. (Table 2)

Clinical Features:

	Frequency (n=76)	**Percent**
Symptoms		
Eye pain	76	100
Eye redness	70	92.11
Blurred vision	76	100
Sensitivity to light	56	73.68
Excessive tearing	61	80.26
Eye discharge	23	30.26
Signs		
Corneal Opacity	55	72.37
Corneal Vascularization	32	42.11
Ciliary Congestion	76	100
Blepharospasm	76	100
Fungal pathogen causing keratitis		
Fusarium species	49	64.47
Aspergillus species	11	14.47
Candida species	16	21.05
Success Rate %	74	97.36
Repeat Injections %	15	19.73
Mean Healing Time	30 days	

Table 3: Visual Acuity Status:

Visual Acuity, n(%)	***Baseline***	***One week***	***One Month***	***Third Month***
6/6	0	2	10	12
6/9	0	5	14	17
6/12	0	6	25	32
6/18	0	31	6	4
6/24	20	10	8	2
6/36	51	8	6	7
< 6/60	5	14	7	2
Total	**76**	**76**	**76**	**76**

*Data presented as frequencies

Visual acuity was noticed at baseline, one week, one month and third month. At baseline patients came with bad vision 20 patients with vision 6/24, 51 with vision 6/36 and 5 with < 6/60. At third month vision has improved and now 12 participants gain vision 6/6, 17 had vision 6/9, 32 had vision 6/12, 4 with vision 6/18, 2 with vision 6/24, 7with vision 6/36 and only 2 remains vision of < 6/60.

Table 4: Condition of Vision after last follow-up

Visual Acuity, n(%)	frequency	Percent
Improved	63	82.89
Stable	11	14.47
Worse	2	2.63
Total	76	
*Data presented as frequencies and percentages		

Visual acuity status at the last follow-up of the third month showed improvement in visual acuity was seen in 63 (82.89%) respondents, vision remained stable in 11 (14.47%) however 2 (2.63%) had worsened their vision after post intervention.

Discussion

Fluconazole is a triazole antifungal agent that interrupts the conversion of lanosterol to ergosterol which leads to fungal death by affecting the stability of the fungal cell membrane. It is effective in multiple fungal infections due to aspergillus,candida,and fusariumand fungi resistant to natamycin, itraconazole, or amphotericine B. The effectiveness of this drug depends upon its concentration, which means higher the concentration stronger the antifungal effect.[13] This drug has better permibility through the corneal stoma yet its ability to reach corneal tissue is challenging. This leads to prolong treatment and higher chances of recurrence.[14] To overcome this issue and target the corneal stroma directly intrastromal Fluconazole injection has been introduced and being used by many researchers, in this method corneal stroma is directly targeted yet drug efficacy was controversial because of lack of uniformity in the injection application method used in various studies. In this study to avoid this controversy uniform method of intrastromal Fluconazole injection was applied.

There are different types of antifungal drugs and these are used as topical and systemic therapy for the treatment of fungal keratits but we found intrastromal antifungal drug delievery most effective as it was delieverd directly at the target. The urban population has higher incidence as compared to rural likely due the exposure to pollution and it was compared with the studies done by shahbazaslam et al [15] and Gunjan Saluja et al.[16] In Pakistan fungal infection is more common in rural areas due to vegetative trauma.

In a study conducted by shahbazet al in–69% of the patients had full recoveryof vision, quality of life, and pain related complaints. 30% of the patients had no improvement in vision. 1%of the patients had worsening keratitis. This study suggested that topical use of injectable fluconazole is a safe and effective antifungal drug for the treatment of fungal keratitis.

In another study conducted by Gunjan Saluja etal, he studied the efficacy of the intrastromal injection of Fluconazole against amphotericin B, and natamycin in recalcitrant fungal keratitis. The primary outcome was time taken till the complete resolution of infection,but the secondary outcome measure that is best corrected visual acuity was achieved at six months;the mean healing time for intrastromal injection was better than other drugs. Deep vascularization after healing was significantly better in the intrastromal injection. Intrastromal injections were found safe and effective as compared to the conventional therapy in the management of recalcitrant fungal keratitis.

In our study we observed that main symptoms of keratitis are eye pain, red eye ,blurred vision.Corneal opacity is effected 72.37 %, corneal vascularization 42.11% along with ciliary congestion and blepharospasm. The main organism involved was fusarium species 64.47%, aspergillus species 14.47%, and candida species 21.05%. The mean healing time in our study was 30 days which is comparable with the studies conducted in other parts of the county and different countries in the world. A study conducted in Lahore Pakistan the avarege healing time was 21 days. [17] Astudy conducted in india by Kalaisselvi et al, the average healing time was 25 patients was 17 days. [18] Another study by Sharma et al.the mean healing duration was almost 39±7days. [19]

A study conducted by bongomin F et al [20] stated that about 610821 eyes in Pakistan will go blind because of fungal keratitis each year. It has been investigated that 59% of the eyes in Pakistan had a final vision worse than 6/60 and evisceration were necessary in 11% of cases [21] In our study, we observed that on the third month of treatment, there was remarkable improvement in the vision of the patients . Visual acuity status at the last follow-up of the third month showed improvement.

Conclusion: Fluconazole injection observed to be most effective drug to treat fungal keratitis mostly in vegatitive trauma.

Conflict of Interest: The authors decleared that there were no conflict between them.

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