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Effect of Sub-Conjunctival, Topical and Systemic Fluconazole On Refractory Fungal Keratitis

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ABSTRACT

Background: About 40 to 50 percent of all instances of microbial keratitis are caused by fungal keratitis (FK). Untreated FK can lead to corneal damage and endophthalmitis, both of which can lead to irreversible vision loss. Since long-term consequences, including blindness, can be prevented by timely diagnoses and treatment of microbial keratitis, there is no laboratory support for this type of diagnosis. Some experts in the field of ophthalmology have long held that it is possible to discriminate between fungal and bacterial infections of the cornea using clinical indicators.

The aim of the study: It was assessment of the efficacy and safety of topical and systemic and sub-conjunctival fluconazole treatment for refractory fungal keratitis.

Patients and Methods: Eleven people with refractory fungal keratitis took part in this investigation. All cases were managed with topical fluconazole 2% hourly for 2 days, then tapered 5 times/day for one week, sub-conjunctival fluconazole 2mg/ml once for 14 days and oral fluconazole 150mg per week daily. The diagnosis was based on KOH wet mount and clinical signs of fungal keratitis.

Result: The result was eight of patient successfully treated with visual acuity improvement and local nor systemic side effect were observed.

Conclusion: Severe fungal keratitis can be treated with topical and systemic, sub-conjunctival fluconazole, which may reduce the need for surgical intervention.

Keywords: Fluconazole, Fungal keratitis.

INTRODUCTION

Since its first description in 1879, the incidence of fungal keratitis (FK) has steadily risen over the last three decades. It is responsible for 40 to 50 percent of all cases of microbial keratitis[1,2].

In the event that untreated FK does not improve, it might result in corneal damage, endophthalmitis, and permanent vision loss. As a result, the importance of early detection and treatment cannot be overstated[3,4]. It is possible to set off FK in more than one hundred distinct kinds of fungi[5].

There are two types of fungi that cause FK: yeast and filamentous fungi, both of which can be categorized as monomorphic. Personal risk factors, regional temperature, climate conditions, geography, and urbanization all play a role in determining which fungus is responsible for FK[6].

Among the most common causes of fungal infections, trauma, immunocompromised states, ocular surface illness, and contact lens usage are all risk factors for FK [6,7].

Many establishments lack the ability to identify the type of microbial keratitis that is present. Based on the potassium hydroxide (KOH) wet mount data, this opinion is supported. KOH is a simple, affordable, and fast test that has a straightforward interpretation. Before making any clinical judgments, it's critical to test the validity of any such claims. Additionally, antifungal therapy is frequently in short supply and prohibitively expensive[8].

While the KOH has been found to be an excellent diagnostic tool for patients in resource-poor locations, a large South Indian study indicated that the KOH's ability to detect fungus in 1352 patients with culture-proven fungal corneal infection was 91%[9].

Microbial keratitis patients have been thoroughly examined in other investigations to determine the exact aspects of the disease. Satellite lesions, increased slough, dry texture, serrated infiltration borders, hypopyon, anterior chamber fibrin, and colour were some of the other characteristics noted. Fungal keratitis was linked to elevated slough and serrated infiltration margins, while bacterial keratitis was linked to anterior chamber fibrin and raised shed (surface profile)[8].

Objective:

It is to see if topical, systemic, and sub-conjunctival fluconazole are effective and safe in the treatment of refractory fungal keratitis.

PATIENTS AND METHODS

A prospective, interventional, case series study was used. It was carried out between June and December 2020 in Dar Altaimuz Eye Center, Benghazi. Libya. Eleven patients with refractory fungal keratitis had their eyes examined using slit-lamp biomicroscopic examination, and corneal scrapings and potassium hydroxide (KOH) stains were collected from the corneal ulcer for the study.

Sample preparation:

Slit-lamp magnification and topical anaesthetic with 0.4 percent Benoxinate hydrochloride prompted corneal gratings to be collected from the base and edge of each ulcer, which were then transferred to Al-Akeed Lab for microscopy assessment. The presence of fungal

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filaments, hyphae, or pseudohyphae in the preparations was deemed conclusive evidence of fungal keratitis in the patients. In the corneal scrapings, fungal hyphae were referred to as moulds, whereas pseudohyphae were referred to as yeast. Fungal filaments were defined as the following: **(i)** It could be spotted at low magnification (x10) and confirmed at a higher magnification (x40 or x100); **(ii)** only if it showed signs of extensions and septation; and **(iii)** the smear would be considered positive if the spot was located in the centre. Fungi might be detected by looking for a single fungal filament on the entire slide, but without it, a negative result would be reported.

All patients got topical fluconazole 2 percent hourly for two days, then tapered 5 times a day for three weeks, subconjunctival fluconazole 2mg/ml injection. Intravenous fluconazole 2 percent solution up to 1 ml was injected into the inferior temporal and inferior nasal bulbar conjunctiva of the bulbar conjunctiva by insulin syringe, once for 14 days, and oral fluconazole 150 mg per week was taken orally.

Inclusion criteria: included the presence of typical features of fungal keratitis as ulcer with serrated edge, dry texture, hypopyon and satellite lesions. Evidence of filamentous and yeast fungi on smear (potassium hydroxide wet mount) and consent of the patient.

Exclusion criteria: includes evidence of herpetic ulcer, neurotrophic, interstitial, ulcers associated autoimmune disease by history and examination.

Ethical consent:

An approval of the study was obtained from Benghazi University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULT

The demographic data of the eleventh participants by means of age ranged from 40 – 65 year. The mean age was 51 ± 6.16 years. While by means of gender; 27.3% were females and 72.7% were males (figures **1-2**).

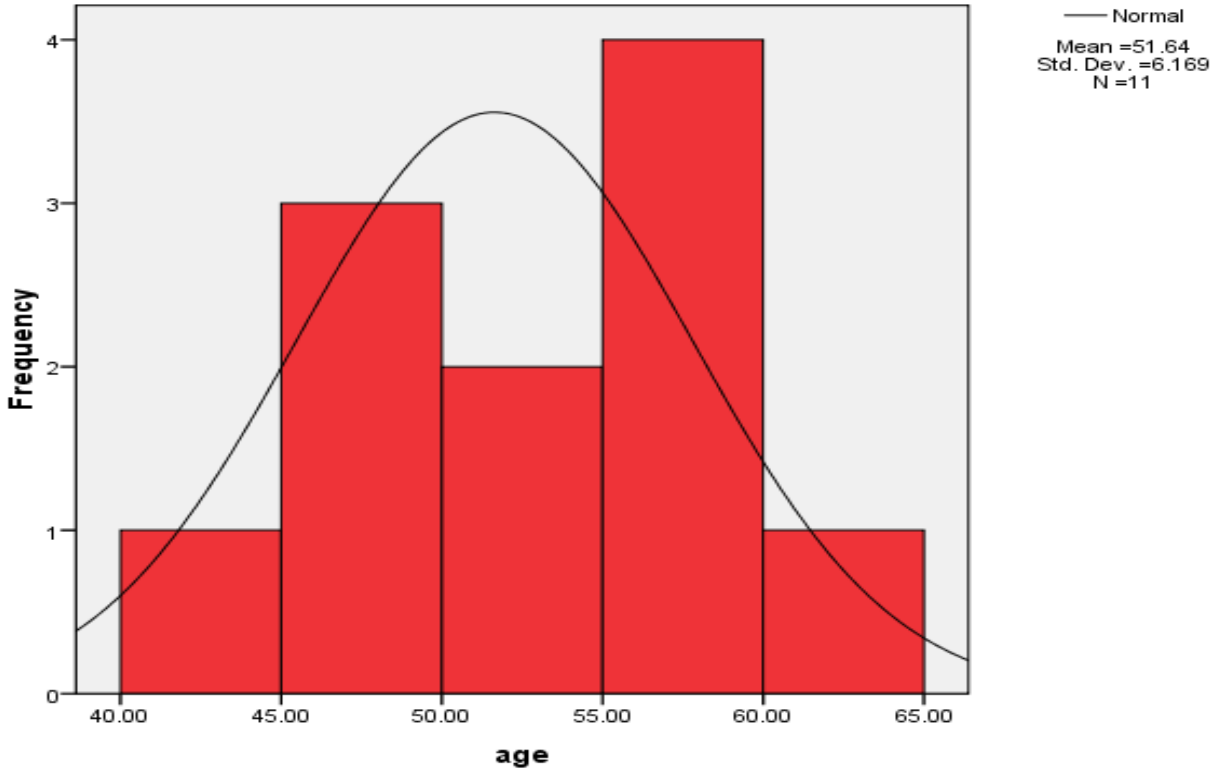

Figure (1): Show distribution of age.

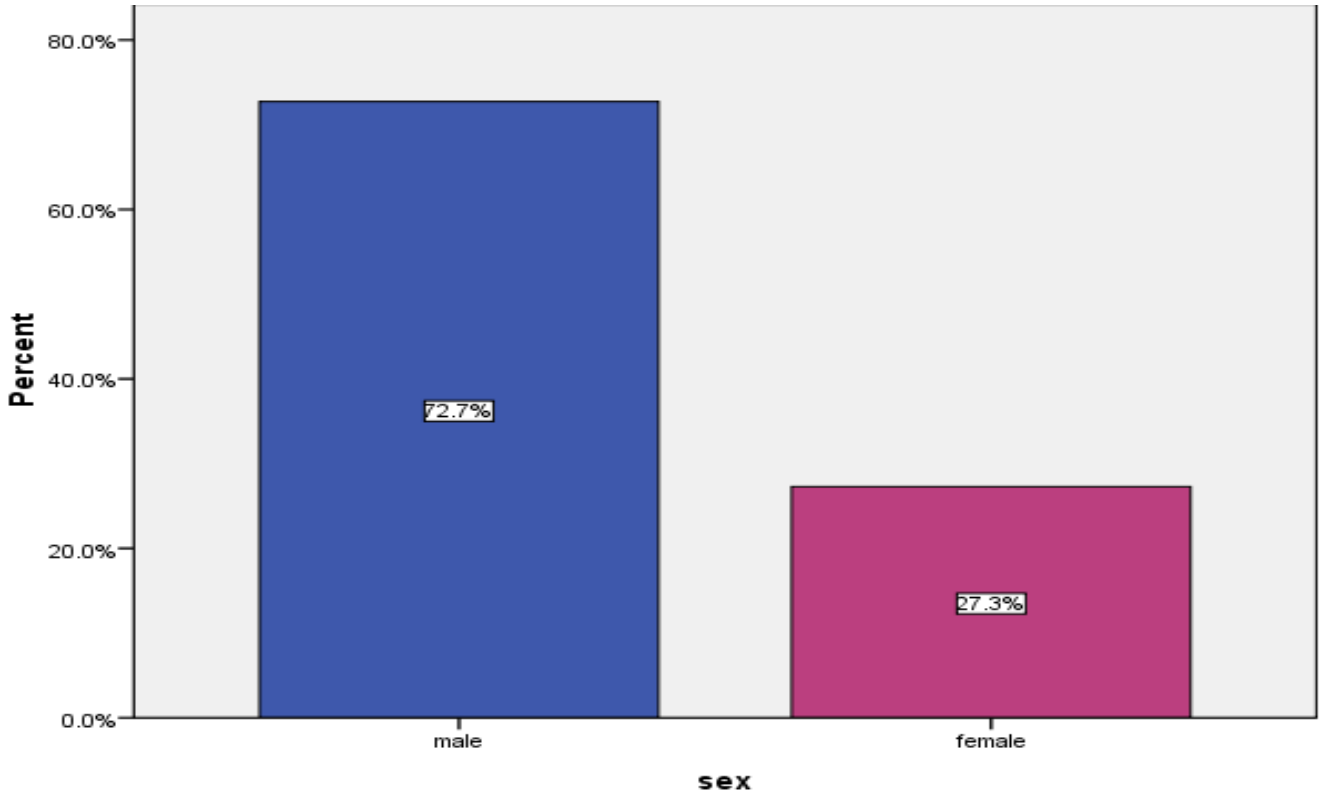

Figure (2): Show distribution of sex.

The ulcer characteristics in which 81.8% with satellite lesion, 72.7% with serrated edge, 63.6% with dry texture, 72.7% with raised edge, 81.8% with hypopyon. The KOH result shows 54.5% candida and 45.4% filamentous (Tables **1**, **2**).

Table (1): Demonstrate the ulcer characteristics.

Variables	Ulcer characteristics			
	Yes	%	No	%
Satellite lesion	9	81.8	2	18.2
Serrated edge	8	72.7	3	27.3
Dry texture	7	63.6	4	36.4
Raised slough	8	72.7	3	27.3
Hypopyon	8	81.8	3	27.3

Table (2): Demonstrate the KOH result.

KOH result	Candida	Filamentous
No.	6	5
Percent	54.5%	45.5%

The visual acuity at the time of presentation in 5 eyes (45.45%) was 6/60, while in 6 eyes (54.45%) is 6/36 on Snellen chart (Table **3**).

Table (3): Demonstrate the visual acuity at the time of presentation**.**

Visual acuity	Logmar +1 (6/60)
No.	5
Percent	45.4%

Figure (**3**) demonstrates the risk factor for the patients were 27.3% had history of trauma, 18.2% immunosuppressive drug and 36.4% of the patient have history of diabetes mellitus.

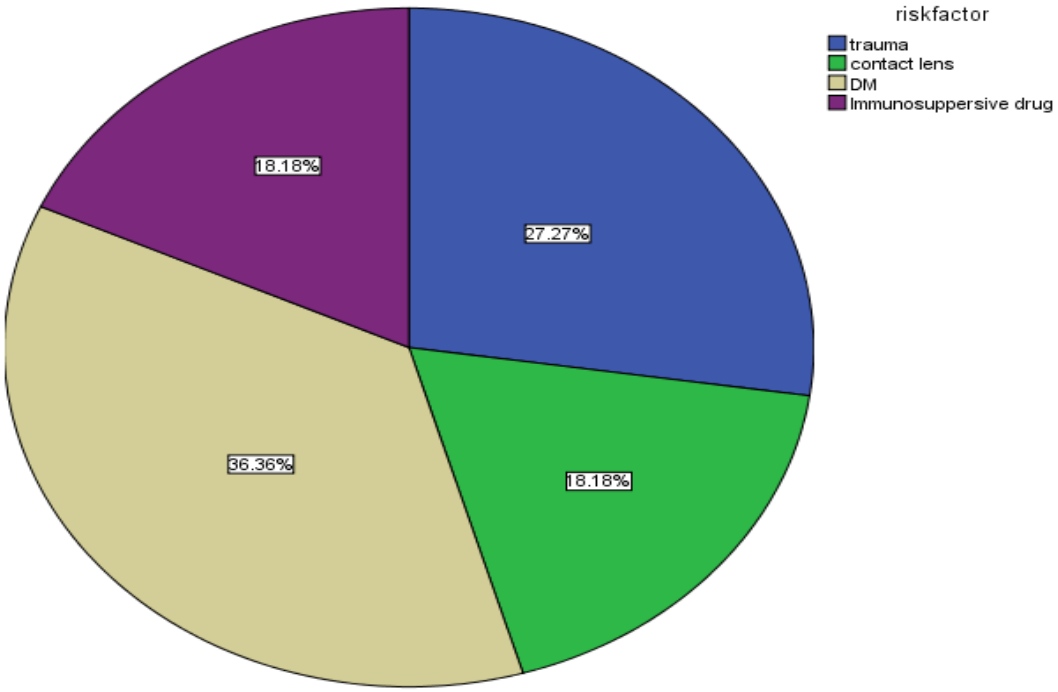

Figure (3): The risk factor for the patients**.**

Table (**4**) demonstrate patients who received treatment before study were (18.18%) received topical combination fungal and antibiotic, (54.54%) received topical, systemic and sub-conjunctival antibiotic only and (27.27%) had not been treated.

Table (4): Demonstrate patient was received treatment at presentation.

Treatment at presentation	Antibiotic/antifungal	Antibiotic only	No treatment
No.	2	6	3
percent	18.18	54.54	27.27%

Table (**5**) responses of the patients to the antifungal agent were 72.7% show good response to antifungal, were 27.7% show no response.

Table (5): Response of the patient to the antifungal agent.

	Frequency	Percent
Yes	8	72.7%
No	3	27.3%
total	11	100.0

Table (**6**) demonstrate healed ulcer (37.5%) of the responded patients healed with central ulcer and (62.5%) healed with mild peripheral ulcer.

Table (6): Demonstrate healed ulcer**.**

	Healed with central ulcer	Healed with peripheral ulcer
No.	3	5
Precent	37.5%	62.5%

Table (**7**) demonstrate visual acuity after treatment was (18.18%) improvement by one line on Snellen's chart, (54.54%) improve by two lines and (27.27%) no improvement.

Table (7): Demonstrate visual acuity after treatment.

Visual acuity	Improvement by one line	Improvement by two line	No improvement
No.	2	6	3
Percent	18.18%	54.45%	27.27%

DISCUSSION

A drug in the azole class, fluconazole is used to treat ocular fungal infections because of its ability to penetrate the ocular tissues[10]. It has been established that fluconazole can attain therapeutic levels of ocular infiltration whether administered topically, orally, and systemically, making it useful for treating various ocular fungal diseases, including superficial and deep-seated mycosis [11,12]. The antifungal activity of this medication, which inhibits fungus cytochrome P-450, has a favourable safety/toxicity profile, high absorption, and potency against Candida and Aspergillus spp[13,14)].

Animal studies using intravitreal fluconazole injection demonstrate low ocular toxicity in comparison to studies using other drugs, such as amphotericin B [15]. Fluconazole's uptake was shown to be quick, according to the results of fluconazole penetration. Most antifungal drugs cannot penetrate the corneal epithelium, which serves as a significant barrier [16]. Epithelial debridement can lead to significant issues, such as perforation or aggravation of the ulcer, especially in fragile corneas with fungal keratitis, even if the epithelium is intact and removal is desirable. It's also been shown that fluconazole permeated equally well into the cornea and aqueous of both corneas that had been debrided and those that had not been debrided [17]. Fluconazole's potential as a subconjunctival agent has yet to be realized in clinical practice. Fluconazole treatment in the subconjunctival area after penetrating keratoplasty is favourable, according to one study.

Fluconazole's effect on patients with Aspergillus species and Candida keratitis with hypopyon was examined in this study. Due to a lack of availability in our nation, conventional topical anti-fungal agents such as natamycin 5 percent or amphotericin B could not be administered. This improvement was noted on the second and seventh days, respectively, for three eyes infected with Candida albicans and five eyes that had been infected with this bacterium. Treatment with fluconazole for severe keratomycosis with hypopyon has prevented keratoplasty as a major mode of treatment because no clinical evidence of corneal decomposition or conjunctival ischemia was observed in any patient even after repeated injections.

CONCLUSION

Fungal keratitis can be effectively treated with topical and systemic, sub-conjunctival fluconazole, and the dose utilized in this trial appears to be both safe and efficacious.

Conflict of interest: The authors declare no conflict of interest.

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Author contribution: Authors contributed equally in the study.

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