Management of Mycotic Keratitis

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Citation

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Abstract

Objective: To evaluate a new treatment regime in cases of mycotic keratitis.

Design: A series of consecutive fungal corneal ulcer cases studied for clinical and pathological results, which attended hospital in a period of sixteen months, following combined use of two topical antifungal drugs, namely fluconazole and natamycin along with chemical cautery by pure carbolic acid and povidone iodine.
Participants: Forty two consecutive patients of fungal corneal ulcer were studied which attended the department of ophthalmology, R.D.Gardi Medical College hospital during April 2005 to August 2006.
Methods: Diagnosis was confirmed by detail history, slit lamp examination and, microscopic examination of corneal scraping for fungal hyphae and culture of fungus. Anterior chamber tap was done in cases of hypopyon and material obtained sent to laboratory for microbiological study. Combined therapy with topical Fluconazole and Natamycin and adjunctive treatment by chemical cautery – phenol and iodine started after confirming diagnosis of mycotic keratitis. The cases were categorized as simple (29- 69.0%) and severe (13-31.0%).

Main Outcome Measures: The primary efficacy criteria were the comfort of patient, remission of signs, reducing of expansion of ulcer, staining of epithelial defect and laboratory negative report for fungus.

Results: Symptomatic improvement observed within 3-5 days and clinical signs by 4th day in simple cases while severe cases took as much as 7-12 days; all cases responded and cure observed in 100% cases; laboratory negative report seen in 3-5 weeks. Comparison with control not done as it not defensible.

Conclusion: This study suggests that in all suspicious cases of fungal corneal ulcer, corneal scraping is mandatory to diagnose mycotic keratitis. Treatment with multi-antifungal drugs along with multi- agents' chemical cautery is effective and safe method

INTRODUCTION

Fungal keratitis is no more a diagnostic and therapeutic challenge if managed properly within time although it is difficult to establish clinical diagnosis, isolating the etiologic fungal organism in the laboratory [1,2,3] and treating the keratitis effectively with available antifungal agents. Moreover incidence of fungal keratitis has increased over the past 30 years as a result of the frequent use of topical corticosteroid and antibacterial agents in treating eye infections and postoperatively [4,5] ; the rise in the number of patients who are immuno-compromised, and better laboratory diagnostic techniques that aid in its diagnosis. Most cases are associated with outdoor agriculture activities [7,8,9] .

Ocular fungal organisms accountable for corneal ulcer are: Moniliaceae (non pigmented filamentary fungi, including Fusarium and Aspergillus species), Dematiaceae (pigmented filamentary fungi, including Curvularia and Lasiodiplodia species) and yeasts (including Candida species). [7,8,9,11]

Many clinical characteristics are not specific to fungal ulcers; therefore antifungal therapy is usually withheld, until a diagnosis is confirmed by laboratory studies. Ideally in all patients with suspected fungal keratitis, initial corneal smears and cultures for bacteria and fungus should be performed. Even at district places it is difficult to diagnose the predisposing factors and specific causative organism in corneal ulcer. A waiting period of 2 weeks is usually necessary for confirmation of specific fungal growth in

culture and drug sensitivity takes much longer time, so it is not of much help to treating surgeon. Although hyphae can be easily seen in wet mount KOH preparations and antifungal treatment can be started by seeing hyphae in corneal scrapings.

The antifungal agents used, in topical or systemic route include polyenes (natamycin, amphotericin B, azoles (ketoconazole, miconazole, fluconazole, itraconazole), and fluorinated pyrimidines (flucytosine). Natamycin has a broad-spectrum of activity against filamentous organisms [12], while Amphotericin B is the drug of choice in fungal keratitis caused by yeasts. Application of Betadine povidone iodine, phenol (carbolic acid) directly on infected corneal ulcer enhances healing process [11] and it penetrates deeper tissues. Although cautery agents are effective against all types of organisms but anti-fungal drugs have their own limitations.

The authors have evaluated a therapeutic regime by simultaneous use of topical Fluconazole and Natamycin along with repeated cauterization by Carbolic acid (Phenol) and Iodine (Povidone Iodine) for treating mycotic corneal ulcer. The results are promising without any side effects or inter-drugs reactions. Final outcome were quick healing and preventing of spreading of ulcer which otherwise may results in formation of large corneal opacity and blinding complications. Fungal organisms can extend from the cornea, can cause severe disastrous infections of neighboring structures resulting to scleritis, endophthalmitis, or panophthalmitis, very difficult to treat and result in stern visual loss or even loss of the eye. A safe and not much cumbersome method is suggested which preserve and restore sight; improve vision from the time patient seen at first visit to hospital.

MATERIALS AND METHOD

Forty two patients of fungal keratitis out of total two hundreds and one consecutive corneal ulcer cases were studied which attended the department of ophthalmology, R.D.Gardi Medical College hospital in a period of sixteen months. Detail history taken, clinical examination, slit lamp examination, fluorescein staining and pathological examination done to establish diagnosis of mycotic keratitis. Along with the presenting symptoms a history taken whether resident of urban or rural area, occupation, working conditions, outdoor eye trauma, trauma caused by foreign body in eye, type of foreign body : organic or non- organic, and inquire about possible risk factors like contact lens wearing and prolonged use of cortisone.

Anterior segment examined by slit lamp for ciliary or mixed congestion, size and site of epithelial defect, margin of ulcer, texture, suppuration, deep stromal infiltration, pigmentation, associated endothelial plaque, neovascularization, satellite lesions, anterior chamber reaction, hypopyon and fluorescein staining of epithelial defects.

Diagnosis of mycotic keratitis was done by wet mount KOH preparations of corneal scrapings and fungus growth on suitable culture medias. All patients were admitted in hospital, visual prognosis was explained and they were started on oral ciprofloxacin (500mg BD), non-steroid anti-inflammatory drugs along with supportive treatment e.g. high protein diet and oral vitamin C (500 mg OD), and I.M. injection of vitamin A 40,000 I.U. was given. Topical 0.3% tobramycin drops (6 hourly), 5% natamycin drops (6 hourly), 0.3% fluconazole drops (6 hourly), atropine ointment 1% (BD) instilled. Oral fluconazole 150 mg. B.D. for seven days was given only in severe cases having hypopyon and endophthalmitis.

Cautery by pure (100%) carbolic acid (Phenol) was done at the time of presentation under strict aseptic condition after epithelial debridement in all cases. Subsequently conjunctival sac wash done with povidone iodine, twice in a day by putting two drops of Povidone Iodine on ulcer area, let it remain for one minute and then washed with bland lotion. Carbolic cautery was repeated only in severe cases on every third day. Iodine wash was not done at the time of carbolic cautery.

The patients were discharged after three to nine days of hospitalization when their symptoms abolished and visual acuity improved. They were advised to continue treatment with topical drugs for further two weeks. Follow up was done at weekly interval for 1 month, subsequently monthly for three months.

Main Outcome Measures: Symptomatic improvement, comfort of patient, remission of signs, reducing of expansion of ulcer, improvement of visual acuity, fluorescein staining of epithelial defect and laboratory negative report for fungus were taken for efficacy criteria for successful treatment

RESULTS

Forty two patients were confirmed to have fungal ulcer by direct examination of corneal scrapings and / or by fungal culture. Presenting symptoms were foreign body sensation,

discomfort or pain in eye, decreased vision, hypersensitivity to light, redness, thick mucoid or muco-purulent discharge with history of trauma or foreign body in eye. 15 (35.7%) patients had non specific signs like ciliary injection, stromal infiltration, anterior chamber reaction, aqueous flare, keratatic precipitates, hypopyon and positive fluorescein staining while 27(64.3%) patients had specific signs of mycotic keratitis like feathery margins of infiltrate, rough texture, raised borders, brown pigmentation and satellite lesions. A deep stromal infiltrate with an intact epithelium was present in 4 cases (2.8%).

Fungal hyphae were seen by wet mount KOH preparation in 34 (80.9%) and culture growth present in 37 (88.0%) cases. Patients who have both test positive were 31(73.8%). Out of 34 culture grown 23 (54.7%) had pure fungal growth while 14(45.3%) showed fungus with superadded bacterial infections. Aspergillus fumigatus, Aspergillus flavus, Candida albicans, Curvularia, Penicillium and Fusarium species were the causative organism detected.

The maximal occurrence was seen in the post harvesting period of soybean (November) and wheat (March). Thirty seven (88.1%) patients were either farmers or manual laborers from rural agricultural areas and thirty four (91.8%) of them gave a definite history of antecedent corneal trauma due to vegetable or soil matter. Two (4.8 %) patients were the chronic users of systemic corticosteroid for other ailments and got foreign body in eye. One patient presented with large corneal ulcer with endophthalmitis, she took 6 weeks for healing and absorption of exudative membrane. Final visual acuity was 4/60 after 3 months.

The cases were categorized as simple cases twenty nine (69.0%) where ulcer was not more than 3mm in size, in peripheral corneal area and not obstructing and severe thirteen (31.0%) in which ulcer was more than 3mm in size, in central cornea with or without hypopyon .

The primary efficacy criteria were the comfort of patient, remission of signs, reducing or not spreading of ulcer, staining of epithelial defect and laboratory negative report for fungus. In all cases symptomatic improvement observed within three to five days and clinical signs in four days in simple cases while severe cases took as much as seven to twelve days; All cases responded and healing observed in all cases; laboratory negative report seen in three to five weeks depending on the severity and starting of treatment. Visual acuity improved in all cases 2 to 3 lines in Snellen's chart in twenty nine (69.0%) simple cases while thirteen (31%) severe cases got vision from hand movement to finger counting 2-3 meters. Ultimate corneal opacity was smaller in size and density than the ulcer at the time of presentation.

Figure 1

Figure 1: Clinical progress of total patients

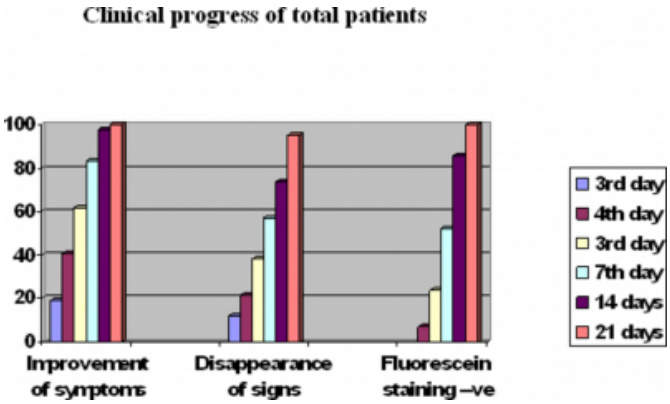


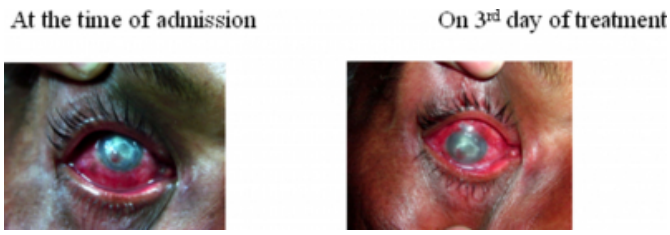
Figure 2

Table 1: Clinical progress of total patients

Days	Remission of symptoms	Improvement of signs	Fluorescein staining –ve
3rd day	08 (19.0%)	05 (11.9%)	---------
4th day	17 (40.4%)	09 (21.4%)	03 (07.1%)
5th day	26 (61.9 %)	16 (38.0%)	10 (23.8%)
7th day	35 (83.3%)	24 (57.1%)	22 (52.3%)
14th day	41 (97.6%)	31 (73.8%)	36 (85.7%)
21st day	42(100.0 %)	40 (95.2%)	42 (100%)

Figure 3

Figure 2: Clinical progress of a case of Mycotic keratitis:



DISCUSSION

Even half millimeter enlargement of central or para-central corneal ulcer in pupillary region may obscure visual axis and reduces visual acuity drastically from 6/6 to F.C. Effectual and intensive treatment is essential and a case of corneal

ulcer with a history of foreign body should be considered as an emergency procedure to avoid future corneal blindness. If diagnosis and treatment is delayed, ulcer extends in surrounding areas, covers a large area which obscures visual axis and the ultimate opacity form after healing leads to loss of sight. In wants of proper diagnosis and management drastic complications like endophthalmitis, panophthalmitis may supervene and loss of eye occurs.

No other treatment is available than keratoplasty for central corneal opacity, which is a cumbersome technique available only at higher ophthalmic centers, have its side effects and complications; at the same time there is always scarcity of donor's cornea and most of the time out of range to common person residing in a village. In this scenario it is better to make corneal ulcer heal as early as possible with all the possible tools available, making the scar as small as possible and trying to retain vision.

Primary mycotic keratitis does occur, but most mycotic keratitis is secondary to some form of trauma to the cornea [9,10] In the present we detected antecedent history of injury or F.B in thirty eight (90.4%), out of which twenty nine(69.0%) due to specific organic matter like thorn, seed-skin, stalk of wheat, soybeans or Babool depending on the harvesting seasons.

To diagnose a mycotic ulcer is not a Herculean job as hyphae can be easily detected in wet mount KOH preparation of corneal scrapping but diagnosis of specific type of fungal keratitis may be problematic because of the very small sample obtained by scraping the corneal ulcer and it takes 2-3 weeks for the fungus to grow in culture. Treatment should be started on the basis of clinical picture and corneal scraping; fungus culture and sensitivity is not of much help to the treating clinician.

Ocular fungal organisms are: Moniliaceae (non pigmented filamentary fungi, including Fusarium and Aspergillus species), Dematiaceae (pigmented filamentary fungi, including Curvularia and Lasiodiplodia species) and yeasts (including Candida species). [7,8,9,11] On culture Aspergillus fumigatus was found to be the commonest causative agent (28.5%) of cases, followed by A. flavus(19.%): Aspergillus species was following by Candida(23.8%), Curvularia (14.2%), Penicillium(11.9%) and Fusarium (4.7%) in our study.

Different species of fungi responds to specific anti fungal drugs. Natamycin is initial drug of choice in for keratitis due to filamentous fungi e.g. Fusarium keratitis, which is available only for topical application.

0.1-0.25% Amphotericin is first agent of choice in corneal infections due to yeasts, such as Candida species [6] . The penetration of topically applied amphotericin B is found to be less than that of topically applied natamycin through the intact corneal epithelium. [12] Fluconazole or ketoconazole should be used in patients with deep stromal keratitis. Chemicals used for cauterization acts against all organisms, go deeper in cornea, act as caustic agent and promotes healing.

Keeping the above discussed views in mind, on clinical suspect of a corneal ulcer to be fungal and on viewing fungal filaments on KOH 10% mount, under microscope, the authors started combined broad spectrum anti- fungal namely natamycin and fluconazole topically. Systemic fluconazole was given only in cases of endophthalmitis. Along with this chemical cautery with pure carbolic acid and povidone iodine was done.

Natamycin is tetraene polyenes. It is most effective against filamentous fungi- namely Fusarium and Aspergillus. It is also effective against Candida, alternaria, Histoplasma, Cldospotium, Phialphora and Actinomyces. It is available as 5% ophthalmic suspension and is given 4-6 times in a day till the ulcer heals. It adheres to areas of ulceration, perhaps increasing the duration of drug contact time. It is generally well tolerated. [16]

Fluconazole is trizole derivative. It has good pharmacokinetic profile and low side effects. It is most effective against yeast, especially Candida albicans as 0.3% ophthalmic suspension, given QID till resolution of ulcer. It has deeper penetration and so is particularly useful in deep abscess. Oral dose of fluconazole is 200-600mgs/day for three weeks in Candida infections.

Chemical cauterization is a traditional technique. Phenol is probably the best agent, but alcohol and iodine can also be used [8] .Carbolic acid has good penetration; it acts both as caustic and an antiseptic. Although the parts touched immediately become white, the normal epithelium rapidly recovers.

Povidone iodine, an iodine releasing polymer has been shown to have strong antibacterial, antiviral and also antifungal properties. [11]

Approximately one third of fungal infections result in either

medical treatment failure or corneal perforation [9] . In our study on using combined broad spectrum antifungal topical eye drops of 5% Natamycin QID and 0.3% fluconazole QID with chemical cautery with 100% carbolic acid and Povidone iodine, in patients with fungal corneal ulcer diagnosed clinically and by positive microscopy in 10% KOH mount, we found encouraging results, prior to confirmation and differentiation of fungus species by culture (which took 2-3weeks)

Symptomatic improvement was observed in 8 cases on 3rd day, 17 cases on 4 th day and by end of week total 35 (83.3%) cases. Clinical signs improved in 24(57.1%) and negative fluorescein 22(52.3%) cases by the 7 th day. After 6-8 days all cases responded although severe cases took up to 6 weeks for complete healing and negative laboratory reports. The end result was much smaller opacity than expected by the size of ulcer at the time admission and complete remission of symptoms.

CONCLUSIONS

The results are promising without any side effects. Final outcome was quick healing and prevention of spreading of ulcer. Thus the following treatment regime is safe and not much cumbersome method, not to mention that it is cheap; which preserves and improves vision from the time the patient first visits hospital. The combined therapy is beneficial is all types of mycotic keratitis even in the places where elaborate investigative facilities are not available.

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