Efficacy of Fluconazole Subconjunctival Injection as Adjunctive Therapy for Severe Recalcitrant Fungal Corneal Ulcer

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Objective: *To assess the efficacy of 0.2% fluconazole subconjunctival injection as an adjunctive treatment in severe recalcitrant fungal corneal ulcer.*

Design: *Retrospective, non-comparative interventional case series.*

Material and Method: *From January 2007 to August 2007, the present study included six eyes of six patients with severe fungal corneal ulcer that did not respond to therapy with topical antifungal drugs, oral itraconazole (200 mg) twice a day and 10 μg intracameral amphotericin B. All of them were treated with 0.5 ml of 0.2% fluconazole subconjunctival injection twice a day as adjunctive therapy for 5 days then once a day till 14 days*

Results: *Three patients were successfully treated within 14 days. Two patients partially responded, and one of them underwent evisceration. The last patient did not respond to treatment and enucleation was done. Severe local and systemic side effects were not found.*

Conclusion: *0.5 ml of 0.2% Fluconazole subconjunctival injection can be a very useful treatment as adjunctive therapy for severe fungal keratitis, with a few mild complications, especially in cases of impending perforation or post operative such as glue application for ruptured cornea.*

Keywords: *Fungal keratitis, Fluconazole subconjunctival injection, Corneal ulcer*

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Infectious keratitis is a major cause of unilateral visual loss in children and adults in developing countries due to corneal scarring, perforation, and loss of visual function(1). Among severe infective corneal ulcer, fungal corneal ulcer is one of the most common in warm-climate countries such as China(2) India and Thailand(3-6). One third of fungal infections result in surgical intervention because of medical failure or corneal perforations(2,8-11). Studies in India(7) and in China(2) indicated that healed and active severe keratitis account for a major proportion of keratoplasty performed. In Thailand, fungal keratitis remains a therapeutic challenge because its management is restricted by the paucity of effective antifungal agents and by the poor penetration of the antifungal agents into the corneal tissue. Another problem is a lack of eye donations. Because of these reasons, fungal keratitis is the most common cause in evisceration and the second cause of enucleation at Mettapracharak hospital (unpublished data during 2002-2006).

Subconjunctival injection of antifungal agents is not commonly used. It is preserved for severe cases of keratitis, scleritis, and endophthalmitis. Although amphotericin B can be given by subconjunctival injection, toxicity is a major problem. Fluconazole is a bis-triazole fungistatic agent that is widely used in Thailand because of less toxicity(12) and cheapness. To the author's knowledge, there are no reports in Thailand about the efficacy and complications of usage fluconazole subconjunctival injection for treatment of severe fungal corneal ulcer which fails to treat with combined treatment including topical, systemic, intracameral antifungal drugs therapy.

Material and Method

The presented study was a hospital-based retrospective, non-comparative interventional case series.

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Table 1. Modification of Jones' grading criteria for severity of corneal ulcer

Factor	Grade 1	Grade 2	Grade 3
Location	Non axial	Central or Peripheral	Central or Peripheral
Area	2 mm	2-6mm	$\geq$ 6 mm
Depth	Superficial one third	Superficial two third	Extending to inner one third
Anterior segment inflammation	Mild	Moderate or Severe fibrinous exudate	Severe hypopyon

From January to August 2007, the author reviewed the outcomes of fluconazole subconjunctival injection for treatment of severe fungal corneal ulcer that did not respond to previous treatment. Each case was diagnosed as grade 3 of severity according to the modification of Jones' grading criteria(6) (Table1).

Inclusion criteria

1. Patients with fungal corneal ulcer who were admitted to Mettapracharak Hospital and had failed the treatments with combined antifungal drugs.

Exclusion criteria

1. Patients who were allergic to fluconazole.

Data obtained from hospital records include

1. Demographic data (e.g. age, sex, gender), predisposing factor, history of treatment before hospitalization, medication and surgical intervention before subconjunctival injection
2. Ocular findings by slit-lamp biomicroscopy and collected characteristics of the ulcer.
3. Results from direct smear examination and culture of cornea scrapping, results of culture and histopathological examination finding, specimens obtained from surgical procedure include aqueous humor tapping, corneal button from penetrating keratoplasty.
4. Results of treatment: The author divided the results into three groups:

Group 1, Response to the treatment was defined as complete eradication of primary infection after subconjunctival fluconazole injection as adjunctive therapy. Infection was considered eradicated in the absence of: recurrence in corneal infiltration, endothelial plaques or hypopyon. Group 2, Partial response to the treatment was defined as incomplete eradication of primary infection. The infiltration, endothelial plaques or hypopyon did not disappear or there was recurrent infection after stopping fluconazole subconjunctival injection. Group 3, Non-response to the treatment was considered when corneal infiltration, endothelial plaques or hypopyon were not improved and progressed to be endophthalmitis or enucleation had to done despite medical intervention.

Initial medical treatments after admission, two kinds of topical antifungal medications (e.g. 0.3% amphotericin B eye drop and fluconazole eye drop) were used in combination. Each patient was instilled one drop of each medication per hour in the day, then one drop of each medication per two hours in the night. They were also given oral itraconazole (200 mg) 1 tab twice daily, 10 μg amphotericin B intracameral once a week. This could be repeated depending on the response of the patients and non-existence risk of corneal perforation. If the clinical did not improve, 0.2% fluconazole 0.5 ml was injected in subconjunctiva at inferior fornix twice a day for 5 days then once a day till 14 days and the patients were followed up for two months after discharge to observe recurrent infection.

Results

Between January 2007and August 2007, 68 patients with a preliminary diagnosis of corneal ulcer were admitted at Metapracharak Hospital. 30 of these patients were diagnosed as fungal corneal ulcer. Six of them failed treatment with combined medical treatments. All of the subjects were classified as grade 3 according to modified Jones' criteria. The majority were male and middle aged population (Table 2), while only one case (case number 6) was female and elderly, with the history of rheumatoid arthritis and dry eye. Their ethnic groups, five of them were Thai, and one was Myanmese, with the mean age of 44.0 years old and range of 29-72 years old. All of them had a history of minor ocular trauma except case 1, who got rupture cornea from a paper stapler (Table 3) and was referred to Mettapracharak Hospital because of retinal detachment and secondary corneal ulcer (Table 2). Topical steroid usage was the common risk factor of the fungal ulcer in Thailand, as the history of case 3. All six patients received treatments from other ophthalmologists before admission with the duration of treatment being a few days to 45

Table 2. The ulcer characteristic and demographic data just before treatment with subconjunctival fluconazole

Patient No.	Sex	Age (years)	Visual acuity	Location	Size (mm)	Depth (Thickness of cornea)	Perforated corneal descematocele	Hypopyon
1	M	38	HM	Peripheral	5 x 4	Endothelial plaque	Penetrating repair wound Post globe	+
2	M	29	HM	Peripheral	2 x 3	>2/3	Thin cornea	+
3	M	30	HM	Peripheral	3 x 3	>2/3	Perforated treat with therapeutic PKP	+
4	M	54	HM	Central	4 x 2	>2/3	Perforated treat with glue application	+
5	M	41	FC 2 ft	Central	5 x 4	>2/3	Thin cornea	+
6	F	72	HM	Peripheral	3 x 3	>2/3	Descematocele	+

PKP: penetrating keratoplasty, M: male, F: female, HM: hand motion CF: counting finger

Table 3. Underlying disease, risk factor, history of treatment before admission and history of treatment before fluconazole injection

Patient No.	Underlying disease	Risk factor	History of Treatment before admission	History of treatment before fluconazole injection
1	None	Rupture cornea from a paper stapler with retinal detachment	ATB 2 days	Ampho ed + Fluconazole ed + Itraconazole (200 mg) 1 twice daily Ampho intracameral 10 µg injection x 1 time
2	None	Trauma by plant leaf	ATB +anti fungal 3 days	Ampho ed + Fluconazole ed + Itraconazole (200 mg) 1 tab twice daily Ampho intracameral 10 µg injection x 2 times
3	None	Steroid usage	ATB + anti fungal 45 days	Natamycin ed + Fluconazole ed + Itraconazole (200 mg) 1 x 2 + Ampho intracameral 10 µg injection x 2 times
4	Pulmonary TB	Foreign body	ATB + anti fungal 30 days	Ampho ed + Fluconazole ed + Itraconazole (200 mg) 1 x 2 + Ampho intracameral 10µg injection x6 times
5	None	Soil foreign body	ATB + anti fungal 14 days	Ampho ed + Fluconazole ed + Itraconazole (200 mg) 1 x 2 + Ampho intracameral injection 4 times
6	Rheumatoid arthritis	Dry eye	ATB + anti fungal 10 days	Ampho ed + Fluconazole ed + Itraconazole (200 mg) 1 x 2 Ampho intracameral injection none

ATB: antibiotic, TB: tuberculosis, ed: eye drop

days (Table 3). Visual acuity was hand motion (HM) in five cases and one was finger count (FC) at 2 ft (case 4). All ulcers that responded to the treatment were found in peripheral corneal.

In this case series, six consecutive patients were different from other studies(13,14). The patients received combined two topical antifungal drugs, oral itraconazole (100 mg) twice daily and 10 µg of intracameral amphotericin B which was used in patients with no precaution such as impending corneal perforation or postoperative condition such as glue application in rupture of descematocele, penetrating keratoplasty (Table 3).

Patients who did not respond to those treatments would be treated by subconjunctival fluconazole (Table 4), the sixth patient in the present study had impending perforated cornea since admission. She was the only one who did not have amphotericin B intracameral injection. Two patients (case 2, 6) and one patient, who got PKP (case 3), were cured. Among the three controlled patients, one was positive for unidentified mold and 2 patients were presumed fungal corneal ulcer. Two patients (case 1, 4) infected with Aspergillus, partially responded to this treatment, one had recurrence after discontinued injection. Mucor infection in the last patient (case 5) did not respond to the treatment and infection progressed so enucleation was performed. All patients who responded to this regimen showed improvement in declining hypopyon level in initial 2-5 days of treatment. Subconjunctival hemorrhage and mild ocular pain were the few clinical complications found after 14 days of treatment. No perforation of cornea or other serious complications occurred during the present study.

Discussion

Fungal keratitis is common worldwide especially in tropical areas and has been known to be the one of the leading causes of all keratitis in developing, agricultural countries(1). Overall incidences of fungal keratitis are different in various studies. It may depend on the referral hospital's position, close to a rural or urban area. In Thailand, the proportion of fungal keratitis from total infectious keratitis was 11.64%- 41.5%(3-7).

The incidence of fungal keratitis among Mettapracharak patients is 44.1% (unpublished data). The presented data is similar to that reported from Chiang Mai(5). It might be that most of the referred patients of both hospitals were from rural areas. Average length of hospitalization in fungal keratitis patients was longer than patients of other infectious keratitis. The main risk factor is minor ocular injuries which is the same as the present study(9-11). Other risk factors were the underlying systemic disease such as Diabetic Mellitus, the underlying ocular disease such as dry eye which was found in the last patient, the topical steroid abuse which was common in Thailand because the patients could buy it without a prescription. In the present study, the third patient bought the topical steroid which might be the important cause of severe fungal keratitis.

Table 4. Result of response to injection, surgical treatment, specimen/culture finding, end result

Pateint No.	Specimen/Culture finding	Respond to injection	Surgical treatment	End result
1	Corneal scraping: neg Vitreous C/S: aspergilous	Partial response decrease Hypopyon level but persistence till 14 day	Remove Hyphema + silicone oil with ampho irrigate in ant chamber	Phthisis bulbi (because retinal detachment surgery failure)
2	Corneal scraping: neg Aqueus humor C/S: neg	Response to treatment Controlled infection	None	Heal with scar VA 20/200
3	Corneal scraping: neg Corneal button C/S Unidentified mold	Response to treatment Controlled infection	Penetrating keratoplasty before subconjuctival injection	Therapeutic graft failure VA HM
4	Corneal scraping: neg Aqueous/aspergilous	Partial response Hypopyon disappeared in 14 days, Reinfection 3 days after stop injection	Evisceration	Evisceration
5	Corneal scraping: neg Corneal button histopathology/mucor	No response	Enucleation	Enucleation
6	Corneal scraping: neg	Response to treatment Controlled infection	none	Corneal scar VA FC 3 ft

FC: finger count, C/S: culture sensitivity

The medical management for fungal keratitis is not sufficient because of limitation of antifungal drug groups, poor drug penetration into the intact corneal epithelium(12) and drug toxicity in prolonged treatment. Medical treatment failure in fungal keratitis may end up with surgical interventions such as PKP, enucleation or evisceration.

Some studies showed 26-36% of fungal keratitis patients received PKP(2,8,9-11) which were usually done in tertiary hospitals(9) with adequate ophthalmologic specialists and effective surgical instruments. Six patients were included in the present study. Patients were mostly referred from urban hospitals and patients had severe infection and could not be controlled with the medical treatments. Therapeutic PKP is an effective procedure for eradicating the infection and preserving the globe integrity(9,10,16,17). However, in Thailand corneal graft is not enough. The patients have to wait for a donor graft at least 1-1.5 months. Thus, some patients with severe progressive lesions have to have evisceration or enucleation performed before getting corneal grafts from donors.

In Mettapracharak Hospital, the fungal keratitis is the most common cause of evisceration and the second most common cause of enucleation following endophthalmitis (unpublished data from 2002-2007). The presented data has a similar trend as the report from a tertiary eye care hospital from China(9) which included a total of 604 fungal keratitis patients, 3% received evisceration and 1% underwent enucleation. These data showed that fungal corneal ulcer was a common serious eye problem in tertiary care hospitals. Obviously many ophthalmologists in many countries(2,8-11) have to face medical treatment failure of fungal keratitis. Patients with failure of treatment had impaired visual function and low quality of life resulting in public health and socioeconomic problems in the country. Fungal keratitis invaded anterior chamber required more concentration of antifungal drug. Subconjunctival route is a method to increase drug concentration in the anterior chamber(17). There were only a few reports about clinical usage of subconjunctival antifungal drug(9,13,14). Yilmaz et al(13) reported 13 patients receiving subconjunctival fluconalzole injection. They found six patients healed in 5 days, six patients improved within 14 days and one patient underwent enucleation. Antifungal drug, Amphotericin B and Natamycin were unavailable in the study. Sachin Dev et al(14) included 33 patients resisting the combined two topical antifungal drugs and Itraconazole eye ointment. This regimen, 0.5 ml of 0.2% fluconazole subconjunctival injection was done once daily. 54% (18/33) of the patients were cured with no recurrence. In cases of Fusarium (68%), Aspergillus (50%) and Culvuralia (100%) were treated successfully by subconjuctival fluconazole injection. Both reports did not use intracameral amphotericin B before treatment with subconjuctival fluconazole. In Thailand, to the author's knowledge, there have been no reports using subconjunctival fluconazole for treatment of severe fungal corneal ulcer.

In the presented study, 50% of patients were cured. In 83.3% of all patients, infections were successfully controlled while they were treated by 0.2% fluconazole subconjunctival injection even when the patients were treated by combined antifungal drugs including intracameral amphotericin B. It was beneficial in patients awaiting corneal graft donor and nearly perforated cornea.

Although the result showed remarkable success of subconjunctival fluconazole injection in treating fungal keratitis, there were some limits in the present study. First, the cultures from corneal scraping were not positive in all patients. The reasons might be from the very deep infiltration and thin corneal surface in most of the patients, corneal scraping had to be done carefully without inducing corneal perforation, and the patients were treated with antifungal drugs before they came to Metthapracharak Hospital. Corneal biopsy and aqueous fluid cultures are usually done in cases with the specific indications and only in the operation rooms. Despite aqueous culture in two patients from the present study, culture showed no organism. Thus, the treatment depended on clinical diagnosis. Second, this regimen required the physician to perform subconjunctival injection and well co-operative patients, compared with using topical eye drops which was much easier done by nurses. Certainly a prolonged period of treatment, results in more complications or drug side effects. Thus, the duration of this regimen was limited to 14 days despite the study by Dev et al(14) reporting the safety of treatment between 11-60 days. Third, the small sample size of the present study and the other pilot study could confound the outcome of the treatment. Further studies about duration of treatment, amount of drug, and frequency must be required.

Fungal corneal ulcer is one of the major eye problems in Thailand. Working adults are most commonly affected and the relative long healing process may affect productivity with consequent of socioeconomic loss. In cases of medications failure include intracameral amphotericin B. Subconjunctival socioeconomic fluconazole injection as adjunctive therapy could be another useful treatment that can be performed easily by a ophthalmologist in primary or secondary care hospital. This regimen could cure and prolong the duration of controllable infection in some cases although there were some limits in the present study.

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