

A clinical study of keratomycosis to compare the efficacy of topical 10% NaCl with 5% natamycin versus 5% natamycin alone as a treatment strategy



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ABSTRACT

Background: Corneal blindness is a major public health problem worldwide and preventable cause of blindness in India. Corneal blindness is the second most common cause of blindness, after cataract, in developing countries. **Aims and Objectives:** A clinical study of keratomycosis to compare the efficacy of topical 10% NaCl with 5% natamycin (Group A) versus topical 5% natamycin (Group B) alone as a treatment strategy. **Materials and Methods:** This prospective, randomized, interventional, and comparative study with parallel design enrolled 100 cases diagnosed with unilateral keratomycosis and fulfilling the inclusion criteria, who presented to the outpatient department of Ophthalmology, Maharani Laxmi Bai Medical College and Hospital, Jhansi, Uttar Pradesh, between April 2021 and June 2022 (15 months). **Results:** Maximum patients in both the study groups belonged to the age group of 41–50 years showed male preponderance and belonged to the low socioeconomic status. Maximum patients in both the study groups had shown total regression in 66 cases with 41 cases from Group A and 25 cases from Group B, respectively. Regression was not seen in 34 cases with 9 cases belonging to Group A and 25 cases belonging to Group B. Maximum patients in study Group A had shown ulcer regression in 3.56 average weeks duration, while it was in 4.50 average weeks duration in Group B. **Conclusion:** This comparative and interventional study demonstrates that the study Group A receiving 10% sodium chloride solution with 5% natamycin helps in faster healing of corneal ulcer, rate of progression of ulcer is slowed down, and complications are less in comparison to Group B receiving 5% Natamycin alone owing to the anti-edema property of hypertonic saline. Hence, topical 10% NaCl solution can be used with 5% natamycin, as a cost-effective adjunct in the management of fungal keratitis.

Key words: Fungal keratitis; Randomized clinical trial; Natamycin

INTRODUCTION

Corneal blindness is a major public health problem worldwide. It is the second most common cause of blindness, after cataract, in developing countries.¹ The WHO estimated incidence of 1.5–2.0 million cases of monocular blindness secondary to corneal ulceration.² Among infectious corneal ulcers, fungal keratitis is the most challenging and most found keratitis in agricultural or developing countries like India.

Keratomycosis is extremely common in tropics and subtropical regions representing important cause of corneal morbidity.

Mycotic keratitis has a worldwide distribution ranging from 17% to 36%. Regional distribution of corneal ulcers in India are as follows: 7.3% in Northern India, 32% in East India, 38.9% in West India, and 32–39.8% in Southern India.^{3–6} The four main fungal genera associated with fungal keratitis are: *Candida*, *Aspergillus*, *Fusarium*, and

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Acremonium. Filamentous fungi such as *Aspergillus*, *Fusarium*, and *Acremonium*, are the major causes of fungal keratitis found in tropical and subtropical regions, whereas *Candida* is predominant in developed countries with temperate climate.

Any breach in the epithelial lining of cornea along with extracellular enzymes such as proteases and collagenases facilitates penetration of fungi further into the stroma damaging the eye integrity and invasion of the anterior chamber heralds the onset of complications.

Fungal infections of the cornea remain a therapeutic challenge due to interplay of various factors such as delayed presentation, chronicity of the infection, resistance to antifungal agents, resemblance to other forms of stromal keratitis, and superadded bacterial infections.^{7,8}

Clinical features

1. Pain
2. Foreign-body sensation
3. Watering
4. Photophobia
5. Blurred vision
6. Redness of eyes.

Signs are more prominent than symptoms in case of fungal corneal ulcer

- Ciliary flush and flare in anterior chamber
- Epithelial surface – dry, rough texture, and dirty gray–white colour
- Delicate feathery branching hyphae with surrounding stromal infiltrate
- Fine or coarse granular infiltrates within the epithelium and anterior stroma
- Stain positive ulcer using fluorescence dye stain
- Multifocal suppurative microabscesses or satellite lesions
- Fungi invade the anterior chamber through intact Descemet's membrane and result in a fixed sterile hypopyon
- In advanced cases, cornea become yellow-white. Stromal ulceration and necrosis may lead to perforation and endophthalmitis.

Natamycin

- Natamycin - tetraene polyene antibiotic derived from *Streptomyces natalensis*
- *In vitro* activity against yeast and filamentous fungi including *Candida*, *Aspergillus*, *Cephalosporium*, *Fusarium*, and *Penicillium*
- Mechanism of action – It binds to the sterol moiety of the fungal cell membrane
- The polyene esterol complex alters the permeability

of the membrane producing depletion of essential cellular constituents.

Side effects of natamycin

1. Allergy, chest pain, dyspnea, paraesthesia
2. Hyperaemia, watering, irritation, pain, corneal opacity.

Role of 10% sodium chloride in keratomycosis

- Therapeutic efficacy of 10% sodium chloride solution is attributed to its anti-edema property
- Topical 10% sodium chloride solution can be used along with 5% natamycin, as a cost effective adjunct in the management of fungal keratitis.

Aims and objectives

Aims

The aim of the study was to compare the efficacy of topical 10% NaCl with 5% natamycin versus topical 5% natamycin alone as a treatment strategy in keratomycosis.

Objectives

- To study the efficacy of topical 10% sodium chloride solution as a useful adjunct to topical 5% natamycin in the management of keratomycosis
- To study the role of 10% sodium chloride in reducing corneal edema
- To signify its role in quickening ulcer regression.

MATERIALS AND METHODS

This prospective, randomized, interventional, and comparative study with parallel design enrolled 100 cases diagnosed with unilateral keratomycosis and fulfilling the inclusion criteria, who presented to the outpatient department of Ophthalmology, Maharani Laxmi Bai Medical College and Hospital, Jhansi, Uttar Pradesh between April 2021 and June 2022 (15 months).

Inclusion criteria

- Age ≥ 18 year and ≤ 70 year
- All the patients with unilateral corneal ulcer
- Patients who followed up for a minimum period of 3 months
- Risk factors such as accidental injury to vegetative matter, farmer community
- Smear and culture confirmed fungal corneal ulcers
- Corneal ulcers with corneal edema and stromal involvement
- Corneal ulcers within a week of onset.

Exclusion criteria

- Age ≤ 18 year and > 70 year
- Refused giving proper consent
- Ulcers of other etiology

- Ulcer with impending or actual perforation, corneal melting
- Patients with loss to follow-up
- Ulcers with bacterial superinfection
- Predisposing systemic illness such as uncontrolled diabetes mellitus
- Cases who had received some treatment outside.

Assignment

- Group A - 50 cases of corneal ulcer, treated with the combination of topical 10% NaCl one drop 6 times per day for 6 weeks with 5% natamycin one drop hourly for the 1st week, every 2 h for next 2 weeks, and then 6 times a day for the next 2 weeks
- Group B - 50 cases of corneal ulcer, treated with topical 5% natamycin one drop hourly for the 1st week, every 2 h for next 2 weeks, and then 6 times a day for the next 2 weeks
- Both groups received 2% homatropine eye drop one drop twice daily, eye drop carboxymethyl cellulose 0.5% 1 drop 4 times a day, tablet fluconazole 150 mg BD for a week, tablet zerodol-SP 1 tablet BD.

Statistical analysis

The data were summarized as mean values with standard deviations (SD). The statistical analysis will be performed using the Student's t-test and the Chi-square test. The SPSS 11.0 for Windows computer software (SPSS Inc) will be used for statistical analysis. $P < 0.05$ will be considered statistically significant.

Assessment

- The size, shape, and depth of stromal involvement of the ulcer were recorded in the case sheet. The presence or absence of satellite lesions, immune ring, stromal abscess, corneal edema, and anterior chamber reaction were also recorded and documented.

Follow up

- All cases were followed biweekly for 6 weeks using slit-lamp biomicroscopy. Signs of regression and progression were carefully looked for and recorded.

Regression

- Symptomatic benefit to the patient
- Resolution of infiltrates
- Epithelial regrowth
- Resolution of stromal edema.

Progression

- Worsening symptoms
- Advancing infiltrates
- Increase in stromal edema

- Formation of stromal abscess
- Descematocele formation.

RESULTS

The results of the study are summarized as: –

1. Maximum patients in both the study groups belonged to the age group of 41–50 years (30.00% in Group A and 26.00% in Group B) (Table 1)
2. Both the study groups showed a male preponderance (70.00% in Group A and 66.00% in Group B) (Table 2)
3. Maximum patients in both the study groups belonged to the low socioeconomic status according to the Kuppaswamy scale (52.08% in Group A and 68.97% in Group B) (Table 3)
4. Maximum patients in both the study groups showed that half (1/2) of the stroma was involved in 53 cases (52% in Group A and 54% in Group B) and 2/3rd of the stroma was involved in 47 cases (48% in Group A and 46% in Group B) (Table 4)
5. Maximum patients in both the study groups had shown total regression in 66 cases with 41 cases (82%) from Group A and 25 (50%) cases from Group B, respectively (Table 5)
6. Regression was not seen in 34 cases with 9 (18%) cases belonging to Group A and 25 (50%) cases belonging to Group B (Table 5)
7. Maximum patients in study Group A had shown ulcer regression in 3.56 average week's duration, whereas it was in 4.50 average week's duration in Group B (Table 6).

Table 1: Age distribution in study group

Age (years)	Total number of patients	Group A (n=50), n (%)	Group B (n=50), n (%)
20–30	10	5 (10.00)	5 (10.00)
31–40	27	13 (26.00)	14 (28.00)
41–50	28	15 (30.00)	13 (26.00)
51–60	22	10 (20.00)	12 (24.00)
61–70	13	7 (14.00)	6 (12.00)

Table 2: Sex wise distribution in study group

Sex	Total number of patients	Group A (n=50), n (%)	Group B (n=50), n (%)
Male	68	35 (70.00)	33 (66.00)
Female	32	15 (30.00)	17 (34.00)

Table 3: Socioeconomic status in study group

Socioeconomic status	Total patients	Group A (n=50), n (%)	Group B (n=50), n (%)
Low	48	25 (52.08)	23 (47.92)
Medium	33	16 (47.06)	17 (50.00)
High	19	9 (50.00)	10 (55.56)

Table 4: Ulcer depth in study group

Ulcer depth	Group A (n=50), n (%)	Group B (n=50), n (%)
1\2	26 (52)	27 (54)
2\3	24 (48)	23 (46)

Table 5: Total regression in study groups

Total regression	Group A (n=50), n (%)	Group B (n=50), n (%)
Present	41 (82)	25 (50)
Absent	9 (18)	25 (50)

Table 6: Regression time (weeks in average) in both groups

Regression time	Total regression (weeks in average)
Group A	3.56
Group B	4.50

DISCUSSION

Corneal blindness constitutes a major public health problem in many developing countries.¹ The WHO estimated that, in every year, about 1.5–2.0 million new cases of monocular blindness in developing countries is secondary to corneal ulceration.

Demographics

Our results are consistent with the finding of Bhushan et al., (2011) -“A study of the pattern and contributory factors of corneal ulcers in Uttar Pradesh and Bihar states of India” where males were more affected with corneal ulcers than females. Rural population was more affected with corneal ulcers than urban, and low socioeconomic strata with poor hygiene was more affected with corneal ulcers than high socioeconomic strata with better hygiene.

In our study, maximum cases of the trauma were due to vegetative matter injury, similar to Sharma⁴ that shows trauma due to vegetative origin as the most predominant cause for fungal corneal ulcer.

Other studies have also found trauma to be the most common predisposing factor in the spectrum of fungal keratitis. The percentage of corneal trauma has been reported to be as high as 42% by Chowdhary and Singh.⁹

On the other hand, in a study conducted at Portsmouth, Southern England, contrary reports were documented and showed that contact lens wear was the main risk factor (31%) for corneal ulcers.¹⁰ This might be due to developing countries involved more in traditional agricultural activities than the developed countries.

Many fungal species can result in fungal keratitis; however, the most commonly implicated are *Fusarium*, *Aspergillus*, and *Candida* species. The causative organism of FK may differ according to several factors including regional temperature, climate, and urbanization. In a study performed in India on FK, *Aspergillus* species were the most commonly isolated species followed by *Fusarium*,¹¹ which is consistent with the results of our study. This was also confirmed in several other studies from India, with one study showing that *Aspergillus* was responsible for more than 55% of all FK cases, suggesting that *Aspergillus* species are the most common cause of FK in the Indian subcontinent¹² according to Saha and Das.

Role of natamycin

- Wang et al.,¹³ found that natamycin was more effective than fluconazole in the management of fungal keratitis, and there was a significant difference between natamycin and fluconazole in cure rate. In addition, the natamycin group was more effective than fluconazole in average period of therapy
- Prajna et al.,¹⁴ concluded that natamycin-treated cases had less chances of perforation or requirement of therapeutic penetrating keratoplasty than voriconazole-treated cases.

Role of hypertonic saline

In our study, the use of 10% hypertonic saline along with topical antifungal natamycin eye drop has proved to be an effective treatment in the management of corneal edema and quickening ulcer regression as seen in our study Group A as compared to study Group B where topical natamycin alone was used as a treatment strategy. Figures 1 and 2 showing effective edema regression after treatment with topical natamycin with 10% NaCl.

Our study with hypertonic NaCl solution gave symptomatic benefit to the patient with corneal edema regression which is same as the clinical pilot study to evaluate the efficacy of a preservative-free hypertonic ophthalmic solution for patients with symptomatic corneal edema¹⁵ where hypertonic saline provided good functional improvement and no adverse effects.

In our study, hypertonic NaCl solution showed a significant decrease in edema which is similar to a prospective study by Knezović et al.,¹⁶ where the efficacy of hypertonic solution correlates with the severity of clinical picture in patients with bullous keratopathy.

Early usage of NaCl hypertonic solution significantly improved the visual acuity and pachymetry readings in Knezović et al.¹⁶

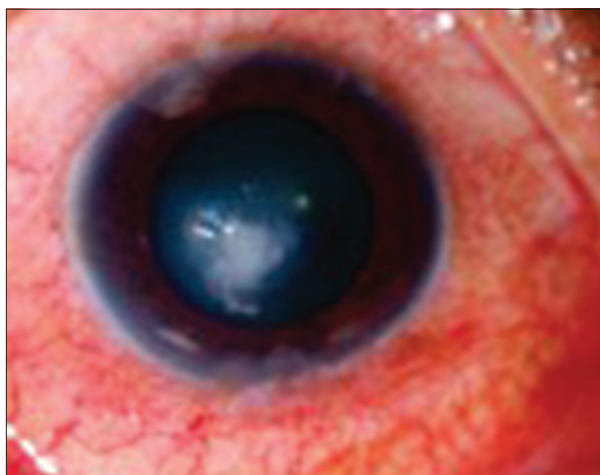


Figure 1: Untreated active fungal corneal ulcer with diffuse circumciliary congestion

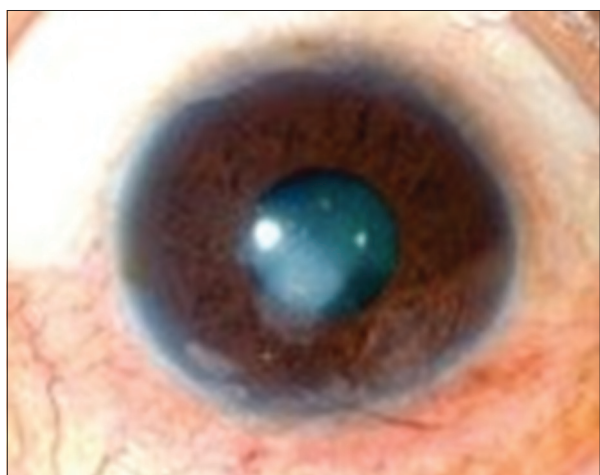


Figure 2: Healed corneal ulcer after 4 weeks of treatment with 5% natamycin and 10% NaCl

Limitations of the study

This was a single-centered study.

CONCLUSION

Corneal ulcer is one of the important ophthalmic conditions causing significant morbidity, especially in developing countries. It constitutes the second most common cause of preventable blindness after cataract in tropical developing countries. This comparative and interventional study clearly demonstrates that the study group receiving 10% sodium chloride solution with 5% natamycin helps in faster healing of corneal ulcer, rate of progression of ulcer is slowed down, and complications are obviously less in comparison to the group receiving 5% Natamycin alone. Furthermore, the number of therapeutic keratoplasties is significantly less compared to the control group. Therapeutic efficacy of 10% sodium chloride solution is attributed to its anti-edema property. Hence,

topical 10% sodium chloride solution can be used along with 5% Natamycin, as a cost-effective adjunct in the management of fungal keratitis.

Early administration of antifungal drugs along with topical 10% NaCl in cases of fungal corneal ulcer may help in faster resolution and prevention of dreadful complications. Corneal ulcers need to be suspected clinically followed by laboratory confirmation and promptly treated with antifungal drugs (topical and/or systemic) and the addition of topical 10% NaCl can prove to be beneficial.

Future prospects need mass awareness in the community regarding the predisposing factors and the magnitude of corneal ulceration in the population at risk (both rural and urban). A large-scale and multicentric study needs to be undertaken in coming time for diagnosis and newer treatment strategies for corneal ulcers.

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Authors Contribution:

JK, NS- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of article; **AJ-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision, design of study, statistical analysis and interpretation, review manuscript, review manuscript, literature survey, coordination, and manuscript revision.

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