Natamycin versus voriconazole for fungal keratitis

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Abstract

Introduction

Infectious keratitis of fungal origin mainly affects people in tropical and subtropical countries, and is an important cause of preventable blindness. Topical antifungals, particularly natamycin and voriconazole, are considered effective, but it is not clear which one is the best treatment alternative.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified three systematic reviews including three studies overall,all of which were randomized trials. We concluded natamycin probably is associated with better visual acuity after infection, and it prevents corneal perforation and/or need to perform therapeutic keratoplasty compared to voriconazole in fungal keratitis.

Problem

Fungal keratitis corresponds to a fungal infection of the cornea, mainly of the epithelium and stroma. The most frequent etiological agents correspond, firstly, to filamentous fungi of the Fusarium, Aspergillus and Curvularia genus, in descending order of frequency and, secondly, to yeasts. In tropical and subtropical countries it constitutes an important cause of preventable blindness, in contrast to what occurs in developed countries, where it scarcely affects the population. The main risk factor corresponds to ocular trauma associated to contamination with plant material, but it has also been associated with the use of corticosteroids, antibiotics, immunosuppressants, chemotherapeutic drugs and ocular prosthetic devices.

There are multiple topical antifungal agents for treatment, such as polyenes (natamycin, amphotericin B), imidazoles (ketoconazole, econazole) and triazoles (fluconazole, posaconazole). The treatment of choice has been for decades topical natamycin, the only antifungal approved by the Food and Drugs Administration (FDA), but the recent emergence of topical voriconazole, a second-generation broad spectrum triazole, has posed new questions, arising thus, the need to evaluate which of these topical antifungals is presented as the best therapeutic alternative.

Key messages

- The use of natamycin in fungal keratitis compared with voriconazole is probably associated with better visual acuity.
- The use of natamycin in fungal keratitis compared to voriconazole prevents corneal perforation and/or need for therapeutic keratoplasty.
- The balance is probably favorable to the use of natamycin in fungal keratitis.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews[1-3] that included three primary studies reported in seven references[4-10], all corresponding to randomized controlled trials.
What types of patients were included*	All trials included male and female patients older than 16 years with an average age of 46.7 years, with microbiological evidence of fungal keratitis; direct visualization of hyphae in corneal scraping by smear with 10% KOH stain or Gram stain[5], smear with 10% KOH stain, Giemsa stain or Gram stain[4] and positive corneal ulcer smear for fungi in patients with visual acuity of 20/40 (0.3 logMAR units) at 20/400 (1.3 logMAR units)[8]. All trials excluded patients who had concomitant corneal coinfection (viral, bacterial or protozoal), signs of imminent corneal perforation or history of corneal perforation[4,5,8]. Two trials[4,8] excluded patients with visual acuity worse than 20/200 (1.0 logMAR units) in the unaffected eye and with bilateral ulcers. Two trials excluded patients without light perception in the affected eye[4,5], and one trial also excluded pregnant patients[4].
What types of interventions were included*	All trials used topical 5% natamycin as intervention: two trials administered 1 drop every hour for 1 week and then 1 drop every 2 hours for 2 weeks (while the patient was awake)[4,8] and one trial 1 drop every hour for 2 weeks[5]. As comparison, topical 1% voriconazole was used: in two trials 1 drop was administered every hour for 1 week and then every 2 hours for 2 weeks (while the patient was awake)[4,8] and one trial administered 1 drop each hour for 2 weeks[5].
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows: • Clinical cure (at 2-3 months) • Time to achieve clinical cure • Visual acuity (at 2-3 months) • Complications of fungal keratitis (corneal perforation, therapeutic keratoplasty, enucleation) • Treatment failure • Adverse effects, including: corneal thinning or descemetocele formation, corneal perforation, endophthalmitis,

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	chemosis, punctate keratopathy, recurrent epithelial erosions, conjunctival injection, ulceration and necrosis of conjunctiva, hepatic and renal toxicity) • Quality of life The average follow-up of the trials was 11.3 weeks, with a range between 10 and 12 weeks.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information about the effects of topical 5% natamycin versus topical 1% voriconazole is based on three randomized trials including 473 patients[5,6,8].
One trial reported clinical cure (30 patients)[5], three trials reported changes in visual acuity (logMAR) and corneal perforation and/or need to perform therapeutic keratoplasty (434 patients)[5,6,8]. The summary of findings is as follows:

- The use of natamycin in fungal keratitis, compared with voriconazole, might be associated with a higher probability of clinical cure, but the certainty of the evidence is low.
- The use of natamycin in fungal keratitis, compared with voriconazole, probably is associated with better visual acuity. The certainty of the evidence is moderate.
- The use of natamycin in fungal keratitis, compared to voriconazole, prevents corneal perforation and/or need to perform therapeutic keratoplasty. The certainty of the evidence is high.

Natamycin versus voriconazole for fungal keratitis

Patients Fungal keratitis
Intervention Topical 5% natamycin
Comparison Topical 1% voriconazole

Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of evidence (GRADE)
	WITH voriconazole	**WITH natamycin**		
	Difference: patients per 1000			
Clinical cure	933 per 1000	998 per 1000	RR 1.07 (0.89 to 1.28)	⨁⨁◯◯[1,2] Low
	Difference: 65 more (Margin of error: 103 less to 261 more)			
Change in visual acuity (LogMAR)**	-0.55 units	-0.67 units	--	⨁⨁⨁◯[2] Moderate
	DM: 0.12 units better (Margin of error: 0.06 worse to 0.31 better)			
Corneal perforation and/or need to perform therapeutic keratoplasty	206 per 1000	126 per 1000	RR 0.61 (0.40 to 0.95)	⨁⨁⨁⨁ High
	Difference: 80 less (Margin of error: 10 to 124 less)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).
*The risks **WITH voriconazole** are based on the risks of the control group in the studies. The risk **WITH natamycin** (and its margin of error) is calculated from the relative effect (and its margin of error).

**LogMAR corresponds to the logarithm in base 10 of the minimum angle of resolution (MAR) of an object. The ability to resolve details separated by 1 minute of visual angle equals LogMAR=0 and corresponds to standard visual acuity. Negative values are indicative of better visual acuity and positive values of worse visual acuity. In LogMAR chart each letter has assigned a value of 0.02 LogMAR units; there are five letters per row, so the total visual acuity corresponds to the multiplication between the total letters correctly read and 0.02.
[1] The certainty of the evidence was downgraded in one level due to moderate risk of bias according to what was reported by the systematic reviews.
[2] The certainty of the evidence was downgraded in two levels due to imprecision, since each extreme of the confidence interval leads to a different decision.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary apply to adult patients with filamentous fungal keratitis (Fusarium, Aspergillus and Curvularia genus).

Although the identified trials evaluated only adults, and no evidence was found in adolescent and pediatric patients with filamentous fungal keratitis, it is reasonable to extrapolate these results to those populations, in absence of direct evidence.

These results do not apply to patients with fungal keratitis due to yeast, such as Candida spp.

These results also do not apply to patients with infectious keratitis of bacterial, viral, parasitic, or mixed etiology (for example coinfection due to fungi and bacteria), since the treatment of infectious keratitis depends on its specific cause.

About the outcomes included in this summary

The outcomes analyzed in the summary of findings table are those considered critical for decision-making by the authors of this summary. In general, they coincide with those evaluated in the systematic reviews identified.

The clinical cure outcome was selected because it directly allows to determine the efficacy of the treatment for fungal keratitis.

Visual acuity is the outcome with the greatest clinical importance; it is correlated with severity or improvement of the disease and it is in general the visual result that is most relevant for the patients, since their compromise directly affects the overall functioning and quality of life.

Corneal perforation and/or need to perform therapeutic keratoplasty was selected as the critical outcome in the course of the disease, since its appearance leads to a more severe disease with a high risk of developing fungal endophthalmitis, and in consequence, to the need to establish a more aggressive treatment (including therapeutic keratoplasty).

Balance between benefits and risks, and certainty of the evidence

The use of topical 5% natamycin in fungal keratitis, compared with topical 1% voriconazole, could result in a higher probability of clinical cure, but the existing evidence has certain limitations. However, the use of topical 5% natamycin prevents corneal perforation and/or need to perform therapeutic keratoplasty and is probably associated with better visual acuity compared to topical 1% voriconazole, with high and moderate certainty of the evidence respectively.

Regarding the adverse effects of the treatments, the systematic reviews[1,2] indicated that there were no adverse side effects reported in the three randomized trials evaluated[4,5,8]. The literature reports that topical 5% natamycin is well tolerated at the corneal level, however its prolonged use presents toxicity generally in the form of punctate keratitis. On the other hand, topical 1% voriconazole is well tolerated, with no reports of side effects to its use[11].

The use of topical 5% natamycin in fungal keratitis has greater benefits compared to the use of topical 1% voriconazole, with an equivalent safety profile between both treatments. Therefore, we consider that there is probably a favorable balance between benefits and risks for natamycin over voriconazole.

Resource considerations

Both natamycin and voriconazole are generally high cost treatments, but the treatment of fungal keratitis with natamycin is about half the value associated to the treatment with voriconazole[13]. In addition, considering that the use of natamycin in fungal keratitis compared with voriconazole decreases the number of patients that evolve with corneal perforation and/or need to perform therapeutic keratoplasty, it is likely that the use of natamycin in fungal keratitis is cost-effective compared to the use of voriconazole.

It is important to consider that in health systems with limited resources, it is possible that none of the evaluated alternatives is available, so alternative treatments of lower economic cost and greater availability could be considered, for example amphotericin or chlorhexidine. The comparative efficacy between the latter and natamycin or voriconazole was not evaluated in the present summary.

What would patients and their doctors think about this intervention

Faced with the evidence presented in this article, most patients and clinicians should lean in favor of the use of natamycin over voriconazole in fungal keratitis.

It is important to note that in a context of low resources, probably due to the high cost of natamycin, patients may prefer lower cost treatments, such as amphotericin or chlorhexidine.

Differences between this summary and other sources

The conclusions of this summary agree with those of the systematic reviews analyzed.

The guideline for the management of corneal ulcer of the The World Health Organization developed by the Regional Office for South-East Asia recommends topical 5% natamycin or topical 0.15% amphotericin as the first-line treatment for filamentous fungal keratitis[14]. The American Academy of Ophthalmology (AAO) recommends topical 5% natamycin as the treatment of choice for filamentous fungal keratitis, with the exception of deep or severe infections (due to the low penetration of natamycin), where it is recommended the joint use of topical 5% natamycin with topical 1% voriconazole[15]. The National Health Service (NHS) of the United Kingdom in its guideline about infectious keratitis, recommends topical 5% natamycin as a first line treatment and as a second line topical 0.02% chlorhexidine, topical 1% voriconazole or topical 5% amphotericin[16].

Could this evidence change in the future?

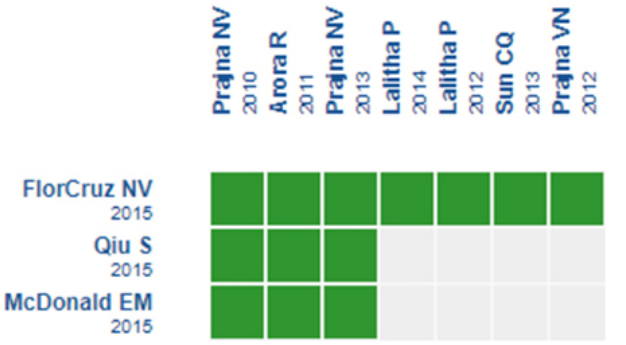
The probability that future research changes the conclusions of this summary regarding the clinical cure and change in visual acuity is high, due to the existing uncertainty. It is unlikely that will change the conclusions about corneal perforation and/or need to perform therapeutic keratoplasty, since its certainty of the evidence is high.

We found one randomized trial not included in the systematic reviews identified, comparing topical 5% natamycin versus topical 1% voriconazole[13].

We did not identify ongoing trials addressing this question in the International Clinical Trials Registry Platform of the World Health Organization.We did not identify ongoing systematic reviews in the International Prospective Register of Systematic Reviews (PROSPERO) of the National Institute for Health Research.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Natamycin versus voriconazole for fungal keratitis.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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