Effectiveness of Voriconazole in Treating Fungal Keratitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT: Antifungal intervention fails in approximately half of fungal keratitis patients, demonstrating its limitations. Voriconazole use for fungal keratitis has raised new interest because of its broad spectrum and good ocular penetration. However, its effectiveness has not been systematically evaluated. Here we try to clarify the benefits of voriconazole in fungal keratitis cases. Randomized controlled trials (RCTs) comparing voriconazole to placebo or other antifungal medications for fungal keratitis were searched in several databases, including PubMed, Scopus, Cochrane Library, ClinicalTrials, and WHO-ICTRP. The primary outcome that analyzed was best spectacle-corrected vision acuity (BSCVA). The secondary outcomes were treatment success, corneal perforation or need for therapeutic penetrating keratoplasty (TPK). From 621 records, nine studies were selected for analysis. The results were as follows: As an initial therapy, topical natamycin outperformed voriconazole in BSCVA (mean difference = 0.14; 95% CI 0.02 to 0.26; P =.03). Voriconazole also has a greater risk of corneal perforation or TPK than natamycin (RR=1.69; 95% CI 1.11 to 2.58; P=.02). As an adjuvant, there is no significant difference found in BSCVA, treatment success, event of corneal perforation, or need for TPK between voriconazole and the other antifungal agents (itraconazole, ketoconazole, amphotericin B, natamycin, and placebo). This study shows that voriconazole is less superior than natamycin in treating early infections of fungal keratitis. More RCTs with larger samples are needed to evaluate voriconazole’s adjuvant efficacy.

Keywords: voriconazole; fungal keratitis; meta-analysis
Effectiveness of Voriconazole in Treating Fungal Keratitis

1. Introduction

In the past decades, the significance of antifungal drugs in the practice of modern medicine has increased dramatically [1]. It coincides with an increase in diseases caused by fungal infections, including those affecting the eye organs. Fungal infections of the eye are serious clinical concerns [2]. Keratitis is a leading cause of monocular blindness worldwide; it is estimated that more than half of corneal ulcers in some areas of the world are due to fungus [3–5]. Fungal corneal ulcers are the second most common cause of mono-ocular blindness in developing countries, after cataracts [6]. Both active and resolved infectious keratitis are significant indications of corneal transplantation surgery [7].

Natamycin (NAT) is currently the first-line therapy for fungal keratitis that has been approved by the US Food and Drug Administration and is available in ophthalmic solution. Having a broad spectrum, NAT is usually used as the first choice in Fusarium infections, it also has good activity against Aspergillus, but less effective in treating Candida infection [8]. However, NAT is only available in suspension preparations and has a large molecular size, causing limited penetration into the cornea. Other antifungal agents with a different route of administration are required to cover the NAT limitation in deep-seated keratitis or with involvement of intraocular structures [9].

Voriconazole (VOR) is a newer generation of triazole antifungal agent that has been widely used for fungal infection. The primary mechanism of VOR is inhibition of ergosterol biosynthesis from fungal cells, causing disruption to the function of the fungal plasma membrane, which in turn will inhibit the growth, proliferation, and lysis of fungal cells [10]. VOR has been gaining popularity for treating ocular fungal infections through the topical, oral, and intraocular routes, owing to its broad spectrum activity, high bioavailability, and permeability across the ocular tissues [7,11,12]. It has been proposed as a good alternative to NAT with minimal toxicity, particularly since susceptibility studies implied that VOR is not only active against filamentous fungi such as Fusarium and Aspergillus, but also against Candida [13–15].

Up to this point, several studies have analyzed and compared the efficacy of VOR to other antifungal agents, not only as an initial therapy but also as an adjuvant for treating fungal keratitis. Therefore, we conducted a systematic and meta-analysis study that contribute to evaluate and conclude the studies relevant to this topic.

2. Method

The systematic review was performed according to the reporting guidelines implied by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the recommendations listed in the Cochrane Handbook [16,17].

2.1. Research question and eligibility criteria

The research question in this study was "the effectiveness of voriconazole therapy in cases of fungal keratitis". The population taken was composed of patients with a diagnosis of fungal keratitis that was proven by direct microscopic examination or culture. Intervention was defined as the administration of VOR in any form compared to a placebo or other types of antifungal agents. We only included randomized controlled trial (RCT) studies with no restrictions on publication date, language, or country. Patients with mixed-infection keratitis were excluded.

2.2. Outcomes analyzed

The primary outcomes of interest were best spectacle-corrected visual acuity (BSCVA) on the final follow-up of the studies reported in log of Minimum Angle of Resolution (logMAR). The secondary outcome discussed in this study were the event of perforation during the study or the need for therapeutic penetrating keratoplasty (TPK), treatment success indicated by complete
2.3. Search strategy and studies selection

Studies were searched from five electronic databases, Medline via PubMed, Scopus, Cochrane Library, ClinicalTrials, and WHO-ICTRP. The last search was conducted on September 26th, 2022. One reviewer (Y.A.A.) developed a search strategy using relevant keywords and using medical subject headings (MeSH) in the form of "eye infections", "keratitis", "fungal keratitis", "mycotic keratitis", "mycotic", "keratomycosis", "filamentous", "candida keratitis", "corneal ulcer", "antifungal agents", "antifungal", "voriconazole", "natamycin", "ketoconazole", "iconazole", "fluconazole", "posaconazole", "itraconazole", "amphotericin B", "caspofungin", "micafungin", "randomized". Search results were pooled, and duplicates were removed.

2.4. Data extraction

Two reviewers independently performed data extraction (Y.A.A., E.A.I.). If the data were unavailable, we contacted the authors via email. We followed up with the initial email if no reply was received after one week. Data extracted were country, study length, sample size and age distribution of the population, antifungal agents used, dosage, and reported outcome. The process of duplication removal and study extraction was carried out using the online software, DistillerSR.

2.5 Risk of bias assessment

Two reviewers (Y.A.A., E.A.I.) used the Cochrane tool for assessing the risk of bias in randomized trials (RoB 2) independently[18]. Five domains of bias were assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. At the end of the judgment, there would be an overall bias. A study with a low risk of bias in all five previous domains was categorized as having a low risk of bias in the overall bias domain. If only one domain has some concerns, there was no high risk of bias in any domain. High risk of bias in the study was judged to be at high risk of bias in at least one domain or if some concerns appear in multiple domains.

2.6 Results and statistical analysis

The extracted data were analyzed using Review Manager for Macbook (RevMan version 5.4.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and forest plots were prepared. Continuous data used for meta-analysis that were presented as median and interquartile range were converted to mean and standard deviation with a calculator in RevMan version 5.4.1. The Mantel–Haenszel random-effects model was used to calculate the risk ratio (RR) and weighted mean difference (WMD), and 95 percent confidence intervals (95% CI) were used. Study heterogeneity was quantified using the I² statistic, which was assessed according to the following criteria: I² less than 25 percent, no heterogeneity; I² of 25–50 percent, moderate heterogeneity; and I² greater than 50 percent, high heterogeneity. A P-value of less than 0.05 indicated a significant difference.

3. Results and discussions

3.1. Study identification

We found 621 articles in the five electronic databases mentioned earlier. After removing duplicates, we screened the titles and abstracts of 427 articles, of which 401 were excluded because they did not meet the criteria of our study. Twenty-six articles were retrieved for full-text review, with 17 being excluded for various reasons. We included nine studies for qualitative synthesis, but only four of them could be meta-analyzed as shown in Figure 1.

3.2 Characteristics of included studies

Table 1 summarized the characteristics of the included studies. Eight of the RCTs included were conducted in India, and one was a joint study.
from India and Nepal. The total number of subjects retrieved from all the studies was 1056 participants.

Five studies analyzed topical VOR [19–23]; three studies analyzed oral VOR [21,24,25]; and two studies analyzed intrastromal VOR [26,27], and they were compared with other antifungal agents. The dosage regimen used in each study was not significantly different. VOR eye drop 1% was used every 1 to 2 hours per day. For oral preparations, a loading dose of 400mg was used two times per day, followed by 200mg the next day. Only one study used a dose of 200mg since the first day [25]. VOR intrastromal concentration 50μg/0.1 mL was used. The studies’ follow-up periods range from 21 days to 6 months.

3.3 Risk of bias assessment

The results of the risk of bias assessment can be seen in Figure 2. In overall bias, there are three
Table 1. Characteristics of studies included in the present review

<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Sample Size</th>
<th>Mean Age</th>
<th>Intervention and Comparison</th>
<th>Dosage</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prajna, 2010*/Ind/</td>
<td>120</td>
<td>46.9</td>
<td>VOR 1%</td>
<td>NAT 5%</td>
<td>NAT 5% and VOR1%: q.1.h. on 1st week, q.2.h. on 2nd and 3rd week”</td>
</tr>
<tr>
<td>Arora, 2011*/Ind/</td>
<td>30</td>
<td>43.1</td>
<td>VOR 1%</td>
<td>NAT 5%</td>
<td>NAT 5% and VOR1%: q.1.h. for 2 weeks, then titrated according to the patient’s response</td>
</tr>
<tr>
<td>Parchand, 2012*/Ind/</td>
<td>45</td>
<td>&gt;18</td>
<td>VOR 1% + VOR 200mg</td>
<td>NAT 5% + VOR 200mg</td>
<td>- VOR 200mg: day one 400mg b.i.d., followed by 200mg b.i.d. - ITR 200mg: b.i.d. - VOR 1%: q.1.h. - NAT 5%: q.1.h.</td>
</tr>
<tr>
<td>Prajna, 2013*/Ind/</td>
<td>323</td>
<td>47</td>
<td>VOR 1%</td>
<td>NAT 5%</td>
<td>NAT 5% and VOR1%: q.1.h. on 1st week, q.2.h. on 2nd and 3rd week</td>
</tr>
<tr>
<td>S. Sharma, 2015*/Ind/</td>
<td>118</td>
<td>41</td>
<td>VOR 1%</td>
<td>NAT 5%</td>
<td>NAT 5% and VOR1%: Day 1–3: q.1.h Day 4: q.1.h. while awake, q.3.h. when asleep Day 5 onward: q.2.h. while awake until cured.</td>
</tr>
<tr>
<td>Prajna, 2016*/Ind/ and Nepal</td>
<td>240</td>
<td>52</td>
<td>NAT 5% + VOR 1% + VOR 200mg</td>
<td>NAT 5% + Placebo</td>
<td>- VOC 200mg: day one 400mg b.i.d., followed by 200mg b.i.d. (20 days) - NAT 5% and VOR1%: q.1.h. on 1st week, q.2.h. on 2nd and 3rd week</td>
</tr>
<tr>
<td>N. Sharma, 2017*/Ind/</td>
<td>50</td>
<td>47.4</td>
<td>NAT 5% + VOR 200mg</td>
<td>NAT 5% + KET 200mg</td>
<td>NAT 5%: q.1.h. for 2 days, then q.2.h until epithelial healing, then q.4.h. for 3 weeks - KET 200mg: q.2.d.</td>
</tr>
<tr>
<td>Narayana, 2019*/Ind/</td>
<td>70</td>
<td>54</td>
<td>NAT 5% + VOR 50μg/0.1 mL</td>
<td>NAT 5%</td>
<td>- NAT 5%: q.1.h. - VOR 50μg/0.1 mL: at day 1, 3, and 5</td>
</tr>
<tr>
<td>Saluja, 2021*/Ind/</td>
<td>60</td>
<td>41.1</td>
<td>NAT 5% + VOR 50μg/0.1 mL</td>
<td>NAT 5% + AMB 50μg/0.1 mL</td>
<td>- NAT 5%: q.2.h. - VOR 50μg/0.1 mL, AMB 5μg/0.1 mL, and NAT(dosage not stated): 1 to 3 times, q.72.h.</td>
</tr>
</tbody>
</table>

VOR=voriconazole, NAT=natamycin, ITR=itraconazole, KET=ketoconazole, AMB=amphotericin B BSCVA=best spectacle-corrected visual acuity, TPK=therapeutic penetrating keratoplasty

studies with low risk [19,24,27], two studies with some concern [22,23], and four studies with a high risk of bias [20,21,25,26].

3.4 Quantitative synthesis (meta-analysis)

The most frequently compared group was topical 1% VOR and 5% NAT, where they used as an initial treatment to fungal keratitis. We conducted a meta-analysis of the four studies comparing these two agents [21,23,25,27]. Clinical improvement was measured based on BSCVA improvement and treatment success. While corneal perforation or the need for TPK indicate treatment failure.
BSCVA outcome. Only three studies could be synthesized for meta-analysis on BSCVA outcome. Two studies from Prajna et al. reported BSCVA three months after treatment [19,22], while Arora et al. reported BSCVA on the final visit [20]. We found that NAT significantly gave a better result in BSCVA compared to VOR (mean difference=0.14; 95% CI 0.02 to 0.26; \( P = .03 \); \( I^2 = 30\% \)) (Figure 3).

Corneal perforation and need for TPK. All nine studies reported the number of corneal perforations during the studies [19–27]. Meta-analysis on four studies compared topical 1% VOR and 5% NAT showed some evidence that VOR has a higher risk of corneal perforation or the need for TPK (RR=1.69; 95% CI 1.11 to 2.58; \( P = .02 \); \( I^2 = 0\% \)) (Figure 4) [19,20,22,23].

Treatment success. No meta-analysis could be performed because all three studies that met our treatment success criteria had a different comparison group [21,23,27].

According to the outcome of the meta-analysis, VOR did not show superior results compared to NAT (Figure 2 and 3). The studies compared VOR and NAT as the initial and sole therapy for fungal keratitis infection. Fusarium was identified as the most common fungus causing keratitis in three of the four studies included in the meta-analysis [19,22,23]. Previous studies showed that Fusarium isolates were less susceptible to VOR than to NAT. High MICs for antifungals are needed to treat Fusarium species in general, especially for VOR. This result was consistent in vitro studies as well as in vivo studies [28–31]. Other fungi, including Aspergillus and Candida species, are more susceptible than Fusarium species to azoles, particularly VOR [31].

Several studies have shown that an individu-
al’s ability to metabolize drugs via the CYP2C19 P450 enzyme influences the pharmacokinetic variability of VOR. Polymorphisms in the gene encoding this enzyme are common, resulting in variable VOR metabolism rates. This polymorphism differs across races, with Caucasians having greater metabolic ability than Asians. Decreased metabolism or absorption related to genetic factors or drug interactions may result in insufficient exposure of the treatment to the fungal pathogen [32]. The majority of the studies examined in this study took place in India, a tropical and developing country where fungal keratitis is usually common. Based on the theory above, these studies findings could likely to differ in other locations where the majority of subjects are Caucasian. However, we haven’t found any comparative study on VOR conducted in any country other than one in Asian region. It is understandable because the urgency to conduct a study on fungal keratitis is low because it is less common in temperate and developing countries, where the majority of Caucasians live. It showed from the report from recent systematic review that estimated annual incidence ranged from 73 per 100,000 in South Asia to just 0.02 per 100,000 in Europe [33].

### 3.5 Qualitative synthesis

The qualitative synthesis only described the findings of the included studies that analyzed and compared VOR to other antifungal agents. Due to the limited number of RCT studies and for most comparisons only one small trial was available, the data could not be meta-analyzed further to improve statistical power. There were five studies with different VOR comparison groups [21,24–27]. All five studies evaluated VOR in oral or intrastromal injection form as the adjuvant to the primary treatment, which was topical NAT. The specific details of the outcomes from the studies are presented in Table 2.

**BSCVA outcome.** Two studies compared oral VOR with placebo; and oral VOR with oral KET,
### Table 2. Outcomes from included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Follow up time</th>
<th>Subject</th>
<th>Corneal perforation/need for TPK</th>
<th>Best Corrected Spectacle Visual Acuity in logMAR</th>
<th>Treatment Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prajna, 2010&lt;sup&gt;20&lt;/sup&gt;</td>
<td>VOR 1% + NAT 5%</td>
<td>3 months</td>
<td>60</td>
<td>60</td>
<td>N=10 NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>VOR had 0.098 better logMAR acuity (nearly 1-line benefit) (95% CI, −0.28 to 0.083;  P=0.29)</td>
</tr>
<tr>
<td>Arora, 2011&lt;sup&gt;21&lt;/sup&gt;</td>
<td>VOR 1% + NAT 5%</td>
<td>Last follow up</td>
<td>15</td>
<td>15</td>
<td>NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>No significant difference between two groups (P=0.227)</td>
</tr>
<tr>
<td>Parchand, 2012&lt;sup&gt;22&lt;/sup&gt;</td>
<td>VOR 1% + VOR 200mg + NAT 5% + VOR 200mg</td>
<td>3 months</td>
<td>15</td>
<td>15</td>
<td>Unavailable</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>NA</td>
</tr>
<tr>
<td>Prajna, 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>VOR 1% + NAT 5%</td>
<td>3 months</td>
<td>161</td>
<td>162</td>
<td>Unavailable</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>VOR had 1.8 lines worse (regression coefficient = −0.18 logMAR; 95% CI, −0.30 to −0.05; P=0.006)</td>
</tr>
<tr>
<td>S. Sharma, 2015&lt;sup&gt;24&lt;/sup&gt;</td>
<td>VOR 1% + NAT 5%</td>
<td>NA</td>
<td>50</td>
<td>60</td>
<td>N=4 NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>NA</td>
</tr>
<tr>
<td>Prajna, 2016&lt;sup&gt;25&lt;/sup&gt;</td>
<td>VOR 1% + VOR 1% + VOR 200mg + NAT 5% + VOR 1% + Placebo</td>
<td>3 months</td>
<td>119</td>
<td>121</td>
<td>Unavailable</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>No significant difference between two groups (predicted BSCVA, −0.02 logMAR; 95% CI, −0.18 to 0.14; P=0.77)</td>
</tr>
<tr>
<td>N. Sharma, 2017&lt;sup&gt;25&lt;/sup&gt;</td>
<td>VOR 1% + VOR 200mg + NAT 5% + KET 200mg</td>
<td>3 months</td>
<td>27</td>
<td>27</td>
<td>N=3 NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>VOR had 0.26 better logMAR acuity (95% CI, 0.04–0.48;  P=0.02)</td>
</tr>
<tr>
<td>Narayana, 2019&lt;sup&gt;26&lt;/sup&gt;</td>
<td>VOR 50μg/0.1mL + NAT 5%</td>
<td>3 months</td>
<td>35</td>
<td>35</td>
<td>N=14 NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>VOR had 0.5 worse logMAR acuity (approx. 1/2 Snellen line) (95% CI, −2.6 to 3.6;  P=0.75)</td>
</tr>
<tr>
<td>Saluja, 2021&lt;sup&gt;27&lt;/sup&gt;</td>
<td>VOR 50μg/0.1mL + NAT 5% + AMB 50μg/0.1mL</td>
<td>6 months</td>
<td>20</td>
<td>20</td>
<td>N=1 NA</td>
<td>NA NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD) or Median (IQR)</td>
<td>No significant difference between three groups (P=0.54)</td>
</tr>
</tbody>
</table>

VOR=voriconazole, NAT=natamycin, ITR=itraconazole, KET=ketoconazole, AMB=amphotericin B  
N=number (frequency), NA=not analyzed, SD=standard deviation, IQR=interquartil range, TPK=therapeutic penetrating keratoplasty,  
CI=confidence interval, OR=odds ratio, HR=hazard ratio
and the results stated there were no significant difference found (95% CI, −0.18 to 0.14; \(P=.77\)) and 0.26 better logMAR acuity in VOR group (95% CI, 0.04–0.48; \(P=.02\)) respectively [24,25]. As an intrastromal injection adjuvant, VOR had no significant difference when compared to topical NAT alone (95% CI, −2.6 to 3.6; \(P=.75\)) and when compared to intrastromal AMB and intrastromal NAT \((P=.54)\) [26,27].

**Corneal perforation and need for TPK.** In the MUTT II study, although the result is not statistically significant, oral VOR reduced the risk for perforation or need for TPK when compared to placebo (HR=0.82; 95% CI, 0.57 to 1.18; \(P=.29\)) [24]. There was also no significant difference in the event of corneal perforation of oral VOR and oral KET \((P=.70)\) [25]. In intrastromal injection form, VOR had a relative hazard of 0.95 for eventuating to TPK versus group with topical NAT alone (95% CI, 0.44 to 2.04; \(P=.90\)) [26]. Other studies stated the number of corneal perforation rates but did not do statistical analysis (Table 2) [21,27].

**Treatment success.** Of the four studies [21,23,25,27] that reported treatment success, three of them met our success criteria [21,23,27]. Sharma et al. found that the percentage of patients receiving NAT was significantly more successful than VOR \((P=.005)\) [23]. More than 90% success was found in all intrastromal VOR, AMB, and NAT groups, but there was no significant difference between the three groups \((P=.80\)) [27]. Parch shown et al. also reported no significant difference shown between the success of the VOR, NAT, or itraconazole (ITR) groups \((P=.90)\) [21].

All studies in the qualitative synthesis section evaluated the role of VOR as an adjuvant therapy to topical NAT. In the oral forms, VOR was compared with oral KET, oral ITR, and placebo [21,24,25]. The majority of the results indicated that VOR has the same efficacy as the other antifungal agents, with no no significant difference found in BSCVA, event of corneal perforation or need for TPK, or treatment success, except for a statistically better BSCVA outcome in the oral VOR group when compared to the oral KET [25]. It should be noted that two of the studies analyzing the efficacy of oral VOR compared to KET and ITR had a small number of subjects with an overall high-risk of bias [21,25].

In a secondary analysis of the MUTT II study, Parchand et al. discovered that *Fusarium* ulcers randomized to treatment with oral VOR in addition to topical NAT and VOR had a lower rate of corneal perforation, smaller scar size, and more rapid reepithelialization [34]. This finding is supported by another study that found that the synergistic action of NAT and VOR resulted in more effective antifungal activity than single-use in vitro treatment in all species tested, implying that these combinations may be useful in the management of fungal keratitis [35].

The efficacy of non-topically administered medications in ocular disease depends on the ability of the drug to cross the blood-ocular barriers, specifically the blood-aqueous barrier during anterior segment disease [36]. Hariprasad et al. reported that orally administered VOR achieves therapeutic aqueous and vitreous levels in the non-inflamed human eye [37]. The concentration of oral VOR obtained from the vitreous in non-inflamed eyes 12 hours after administration exceeds the MIC90 for a wide range of yeasts and molds, but not for *Fusarium* species [38]. However, in an inflammatory state, as occurs secondary to corneal disease, capillaries become more permeable, allowing substances that are normally excluded from the blood-aqueous barrier to enter the anterior chamber, which could potentially have a therapeutic effect [36].

The selection of antifungals in the clinical setting, particularly when administered systemically, must be adjusted to the patient’s condition. The significant toxicity of KET and ITR limits their systemic use in patients with hepatic problems. Hepatotoxicity and liver failure are the most common and serious adverse effects. Therefore, VOR could be a better option because it has milder adverse effects, such as visual disturbances, color vision changes, and photophobia,
which usually subside after 30 minutes [39].

Two studies comparing intrastromal VOR adjuvant to topical NAT alone and other intrastomal adjuvants such as AMB and NAT found no statistically significant difference in any of the three outcomes studied [26,27].

Intrastromal injection may be an effective method of administering antifungal agents. It is capable of increasing local concentrations and is sufficiently effective in eradicating deep corneal infections [40]. However, animal studies revealed that the aqueous humor concentration of VOR decreased rapidly following intrastromal and intracameral injection [41,42]. The decline of VOR in aqueous concentration shows an exponential decay with a half-life of 22 minutes. Although the pharmacodynamics of intrastromal VOR are unknown, these findings suggest that a sufficient level of VOR in the corneal stroma may not be maintained for long after the injection [41]. This might be happened because rapid triazole diffusion was facilitated by low molecular weight for the partially hydrophilic VOR. It contrasts with AMB which has a high molecular weight, where the concentration of intrastromal injection could last above MICs of most fungi for 7 days [42,43].

3.6. Study Limitations

This study has several limitations, one of which is the lack of a study comparison for adjuvant VOR, which limits future analysis. Furthermore, the reporting of outcomes of fungal keratitis treatment is insufficiently standardized, preventing the synthesis of results across studies, despite the fact that there is currently no specific guideline for reporting keratitis studies available. We also do not examine other clinically significant outcomes, such as time to resolution or re-epithelialization, scar size, and complications.

Overall, only a few of the studies analyzed have a low overall risk of bias, which may affect the validity of the results presented. More research is needed to obtain more robust evidence on the benefits of VOR, particularly as an adjuvant therapy, by conducting an RCT with good randomization, follow-up, intention-to-treat analysis, and presenting a complete study outcome. Because each antifungal agent has a unique spectrum of antifungal activity, subgroup analysis of specific antifungal etiologies should be performed to identify the treatment effect.

4. Conclusion

In conclusion, the current study shows that VOR is less effective as an early treatment than NAT, which is still the first-line therapy for fungal keratitis. More large and well-designed RCTs are needed to confirm VOR’s efficacy, particularly as adjuvant therapy in the treatment of deep fungal keratitis or keratitis that does not respond well to first-line therapy.

Competing interests

We declared that all authors have no competing interests to declare.

References

5. Lalitha P, Shapiro BL, Srinivasan M, Ruiz J, Chi-


26. Narayana S, Krishnan T, Ramakrishnan S, Saman-
Effectiveness of Voriconazole in Treating Fungal Keratitis

40. Edwar L, Janna YM, Rozaliyani A, Louisa M. Therapeutic response time of topical voriconazole 1% and intrastromal voriconazole 0.05% versus topical natamycin 5% monotherapy in Fusarium keratitis in rabbit. Mycoses. 2020;63(10):1128–32.