

EFFICACY OF POST-OPERATIVE VORICONAZOLE IN MANAGEMENT OF CHRONIC INVASIVE FUNGAL RHINOSINUSITIS

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ABSTRACT

Background: Chronic invasive fungal rhinosinusitis (CIFRS) is a gradually progressive disease requiring surgical debridement followed by systemic antifungal therapy. There is limited evidence regarding the use of standardized postoperative voriconazole treatment.

Objectives: To assess short-term clinical, endoscopic, radiological and safety outcomes of voriconazole after functional endoscopic sinus surgery (FESS).

Methods: This prospective single-arm interventional case series included 60 patients. Following surgical debridement, participants received oral voriconazole 400 mg every 12 hours for the first 24 hours and 200 mg every 12 hours for two months. Outcomes were assessed over 12 weeks through symptom evaluation, nasal endoscopy, Lund–Mackay scoring, and laboratory monitoring.

Results: Disease control was observed in 48/60 patients (80.0%; 95% CI: 68.2%–88.2%). Resolution occurred in 52/60 patients with nasal obstruction, 42/48 with facial pain, 40/45 with headache, and 43/50 with rhinorrhea. At 12 weeks, 44/60 patients had no visible polypoid. Mean Lund–Mackay score decreased from 16.5 ± 3.2 to 5.8 ± 2.6 . Visual disturbance, elevated liver enzymes, and skin reactions occurred in 8.3%, 6.7%, and 5.0%, respectively.

Conclusion: Combined surgery and postoperative voriconazole were associated with favourable short-term outcomes and predominantly mild adverse effects, although voriconazole-specific efficacy could not be established without a comparator.

Keywords: Chronic invasive fungal rhinosinusitis; functional endoscopic sinus surgery; voriconazole; antifungal therapy; Lund–Mackay score.

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INTRODUCTION

Chronic invasive fungal rhinosinusitis is an uncommon form of invasive fungal rhinosinusitis characterized by a slowly progressive infection in which fungal hyphae invade

the sinonasal mucosa over a period exceeding 12 weeks. Histopathological demonstration of fungal invasion within sinonasal tissue remains central to diagnosis, while vascular, perineural, orbital, or intracranial involvement may occur as the disease advances.^{1,2}

The clinical presentation of chronic invasive fungal rhinosinusitis varies according to the extent of disease. Common sinonasal manifestations include nasal obstruction, discharge, facial pain, headache and altered smell. Advanced disease may produce proptosis, visual impairment, ophthalmoplegia, cranial neuropathies, altered mental status, or focal neurological deficits. Computed tomography commonly demonstrates mucosal thickening, heterogeneous sinus opacification, bony erosion, and possible extrasinus extension.^{1,2}

Management of CIFRS commonly requires a multimodal approach consisting of adequate surgical debridement, systemic antifungal therapy, and correction of modifiable underlying host factors. FESS facilitates removal of infected tissue, improves sinus drainage, reduce fungal burden, and provides tissue for histopathology. Systemic antifungal therapy is subsequently used to treat residual invasive disease and reduce the likelihood of persistence or recurrence.³

Amphotericin B has traditionally been used in the treatment of invasive fungal infections. Its clinical use, however, may be limited by nephrotoxicity, electrolyte abnormalities, infusion-related reactions, and the need for parenteral administration. Voriconazole is a broad-spectrum triazole antifungal agent with high oral bioavailability, favourable tissue penetration, and clinically important activity against *Aspergillus* species. It has consequently become an important therapeutic option for invasive fungal rhinosinusitis. Nevertheless, voriconazole is associated with clinically relevant adverse effects, including visual disturbances, hepatotoxicity, cutaneous reactions and drug interactions, necessitating careful clinical and laboratory monitoring during treatment.^{3,4}

Available evidence suggests that surgical debridement followed by voriconazole may produce favourable clinical, endoscopic, and radiological outcomes in selected patients with chronic invasive fungal rhinosinusitis. Previous case series and comparative observations have reported disease control following combined surgical and antifungal treatment, particularly in less extensive disease and in acute invasive fungal rhinosinusitis.⁵⁻⁷ However, the existing literature is dominated by retrospective studies, small case series, and variable antifungal regimens. Prospective data with a standardized postoperative voriconazole protocol is limited, especially in lower-resource countries where late presentation, lack of access to specialist care, and limited microbiological facilities may affect outcomes of treatment.

It is therefore important to document short-term outcome and safety profile in patients undergoing standard course of FESS and systemic voriconazole. The aim of the present study was to evaluate the clinical, endoscopic and radiological results of postoperative oral voriconazole therapy in patients with CIFRS and to evaluate the incidence of adverse effects in 12 weeks follow-up. Since all participants received both surgical debridement and voriconazole without a comparison group, the study evaluated short-term disease control under the combined treatment protocol rather than the independent efficacy of voriconazole.

METHODS

This prospective, single-arm interventional case series was conducted over six months, after approval from the institutional ethical review board. The study included 60 patients with CIFRS. All eligible participants gave written informed consent which included study

procedures, anticipated benefits, and possible treatment-related risks. The study was conducted in accordance with established ethical principles for research involving human participants.

Patients with suspected CIFRS were evaluated for eligibility. Patients with severe hepatic or renal dysfunction, intracranial extension, intraorbital extension, previous nasal surgery, or a known inability to tolerate voriconazole were excluded.

Sampling technique employed was non-probability consecutive sampling. The sample size of 60 patients were based on the amount of samples needed to estimate a single proportion in accordance with the World Health Organization sample size calculator. An expected favourable treatment outcome of 90%, a 95% confidence level, and an absolute precision of 8% were used in the calculation.

Demographic and clinical data was collected at enrollment with a structured data-collection form. Recorded variables were age, sex, occupation, place of residence, duration of symptoms and presenting symptoms including nasal obstruction, rhinorrhea, facial pain and headache. All patients underwent an otorhinolaryngological examination and baseline assessment of sinonasal disease was made clinically, endoscopically and radiologically. Serum electrolytes, liver-function tests and renal-function tests were taken prior to surgery and all patients were subjected to routine pre-anesthesia evaluation. All participants were operated by a consultant otorhinolaryngologist with at least 5 years post-fellowship surgical experience.

Following surgical debridement, oral voriconazole was initiated using a loading dose of 400 mg every 12 hours during the first 24 hours, followed by a maintenance dose of 200 mg every 12 hours for two months. Participants were clinically observed during the initial period after treatment initiation for acute drug-related reactions. Treatment continuation was accompanied by clinical surveillance and serial laboratory monitoring. Liver-function tests, renal-function tests, and serum electrolytes were performed weekly during the first month and monthly thereafter to identify possible treatment-related toxicity. Participants were also assessed for visual disturbances, cutaneous reactions, gastrointestinal symptoms, and other clinically suspected adverse effects. Patients were followed for 12 weeks after surgery. At each visit, patient was accessed clinically, and endoscopically for disease recurrence, progression and adverse effect of antifungal therapy. The degree of visible postoperative polyposis was graded using the Lildholdt nasal polyp scale.

Radiological burden of disease was assessed by computed tomography (CT) of the paranasal sinuses preoperatively and at 12 weeks, sinus opacification was quantified using the Lund-Mackay scoring system.

The primary outcome assessed was short term disease control with the combined surgical and voriconazole treatment protocol. A favourable treatment outcome was defined as the absence of clinical, endoscopic, and

radiological evidence of progressive or recurrent invasive fungal disease at the final assessment. Persistent disease referred to failure of the original abnormalities, whereas recurrence referred to the reappearance or progression of disease after an initial clinical response.

Secondary outcomes included resolution of symptoms; change in Lildholdt grades; improvement in Lund–Mackay score; and the frequency of treatment-related adverse effects.

Statistical analysis: Data were analysed using IBM SPSS Statistics version 25.0. Continuous variables were assessed for distribution using the Shapiro–Wilk test and summarized as mean ($\pm$ standard deviation) when approximately normally distributed or as median and interquartile range when non-normally distributed. Categorical variables were reported as frequencies and percentages. Symptom-resolution proportions were calculated among participants presenting with each symptom at baseline. Change in the Lund–Mackay score between baseline and 12 weeks was evaluated using a paired-samples test selected according to the distribution of the paired observations. The Pearson chi-square test was used to evaluate associations between treatment outcome and categorical variables when assumptions of the test were met, and Fisher's exact test when any assumption was not met (cell frequencies were expected to be small). The results of all the subgroup analyses were exploratory. Tests performed were two-sided and a p value of < 0.05 was deemed to be statistically significant.

RESULTS

There were 60 patients with CIFRS included in the analysis. The mean ages were 44.2 ± 10.6 years, with the age range reported being 25–65 years. Most participants were aged 41–55 years (43.3%), followed by those aged 25–40 years (33.3%) and 56–65 years (23.3%). The cohort included 38 men (63.3%) and 22 women (36.7%). Thirty-five of the subjects (58.3%) lived in urban areas and 25 (41.7%) were from rural areas. 24 participants reported occupations in the field, 18 in the office, 12 domestic occupations, and 6 other occupations.

At the 12-week assessment, 48 of the 60 participants met the study-defined criteria for short-term disease control, corresponding to an observed success proportion of 80.0% (95% CI: 68.2%–88.2%). Twelve participants (20.0%; 95% CI: 11.8%–31.8%) had persistent or recurrent disease.

Nasal obstruction was present in all 60 participants at baseline and resolved in 52, giving highest symptom-resolution proportion of 86.7% (95% CI: 75.8%–93.1%) followed by resolution in facial pain, headache and rhinorrhea. Because paired symptom-level test results were not available, these changes are reported descriptively rather than as statistically significant improvements. (Table 1)

Table 1. Resolution of presenting symptoms at 12 weeks

Symptom	Present at baseline, n	Resolved at 12 weeks, n (%)	Persistent at 12 weeks, n (%)	95% CI for resolution
Nasal obstruction	60	52 (86.7)	8 (13.3)	75.8–93.1
Facial pain	48	42 (87.5)	6 (12.5)	75.3–94.1
Headache	45	40 (88.9)	5 (11.1)	76.5–95.2
Rhinorrhea	50	43 (86.0)	7 (14.0)	73.8–93.0

Percentages and confidence intervals were calculated using the number of participants with the relevant symptom at baseline as the denominator. Confidence intervals were calculated using the Wilson method.

Table 2. Association of participant characteristics with short-term disease control

Variable	Category	Disease control, n/N (%)	Persistent or recurrent disease, n/N (%)	Statistical test	p-value
Sex	Male	31/38 (81.6%)	7/38 (18.4%)	Fisher's exact	0.744
	Female	17/22 (77.3%)	5/22 (22.7%)		
Age group, years	25–40	17/20 (85.0%)	3/20 (15.0%)	Pearson (χ^2)	0.617
	41–55	21/26 (80.8%)	5/26 (19.2%)		
	56–65	10/14 (71.4%)	4/14 (28.6%)		
Residence	Urban	29/35 (82.9%)	6/35 (17.1%)	Fisher's exact	0.532
	Rural	19/25 (76.0%)	6/25 (24.0%)		
Symptom duration	≤ 8 weeks	30/34 (88.2%)	4/34 (11.8%)	Fisher's exact	0.104
	> 8 weeks	18/26 (69.2%)	8/26 (30.8%)		

Age-group analysis: ($\chi^2=0.965$), ($df=2$). For symptom duration, the relative risk of disease control for presentation within eight weeks versus later presentation was 1.27 (95% CI: 0.96–1.69), and the odds ratio was 3.33 (95% CI: 0.88–12.67).

Endoscopic examination at 12 weeks showed no visible polyposis in 44 participants (73.3%; 95% CI: 61.0%–82.9%). Mild polyposis in 10 participants (16.7%), and moderate polyposis in 6 (10.0%). whereas participant had severe polyposis. Because corresponding baseline Lildholdt grades were not reported, the 12-week distribution is presented as a postoperative status assessment rather than a quantified change from baseline. The mean Lund–Mackay score decreased from 16.5 ± 3.2 at baseline to 5.8 ± 2.6 at 12 weeks, representing an unadjusted mean reduction of 10.7 points and a relative reduction of approximately 64.8% from the baseline mean. A confidence interval, paired effect size, and p-value for this change could not be calculated reliably from the reported marginal means and standard deviations because the within-participant correlation and original paired observations were unavailable.

Most participants, 48 of 60, had no reported voriconazole-related adverse effect during follow-up (80.0%; 95% CI: 68.2%–88.2%). Visual disturbances were reported by 5 participants (8.3%), elevated liver enzymes by 4 (6.7%), and mild skin reactions by 3 (5.0%). No severe adverse effect requiring treatment discontinuation was reported.

As shown in Table 2, disease-control rate do not differ according to gender, age group, residence, symptom duration (all $p > 0.05$). Participants presenting within eight weeks had a higher observed disease-control proportion than those presenting after eight weeks, 88.2% versus 69.2%, respectively. However, this association did not reach statistical significance using Fisher's exact test ($p = 0.104$) and should be interpreted as an exploratory pattern rather than evidence of an independent prognostic effect.

DISCUSSION

The objective of this study was to assess short-term outcome of postoperative Voriconazole in CIFRS over a period of two months. At week 12, 48 of the 60 subjects were disease controlled, and 12 had persistent or recurrent disease. Nasal obstruction, facial pain, headache, and rhinorrhea improved in participants with high baseline scores, and the mean Lund–Mackay score at follow-up was 5.8 ± 2.6 , which is significantly lower than the score at baseline (16.5 ± 3.2). At 12 weeks, most patients did not have any visible polyps, and there was no major adverse effect that led to stopping this treatment.

The observed disease-control proportion was broadly consistent with previous reports suggesting that adequate surgical debridement followed by systemic antifungal therapy can achieve favourable outcomes in selected patients with CIFRS. In a randomized comparison of antifungal agents, Debbarma et al. reported greater short-term clinical, endoscopic, and radiological improvement with voriconazole than with itraconazole or amphotericin B, supporting its potential role in appropriately selected cases.⁸ However, differences in study populations, fungal species, disease severity, surgical completeness, treatment duration, and outcome definitions limit direct comparison. Previous case-based evidence has similarly described successful control of CIFRS after surgery and voriconazole. Turhan et al. reported complete remission in most treated patients, although voriconazole was discontinued in one individual because of visual disturbance and skin rash.⁹ Other published cases have documented favourable responses to voriconazole in chronic invasive fungal sinusitis among patients with human immunodeficiency virus infection, meningeal extension, or refractory invasive aspergillosis.^{10–12} These observations support the biological plausibility and clinical utility of voriconazole but case reports and uncontrolled series cannot establish comparative effectiveness.

Symptom resolution was observed in more than 85% of participants who presented with nasal obstruction, facial pain, headache, or rhinorrhea. Because all participants underwent both surgery and pharmacological treatment, the relative

contribution of each component could not be determined. An endoscopic examination was performed on all the patients 12 weeks later and found that 44 had no polyposis and 16 had mild or moderate polyposis. The Lildholdt scale is a measure of polyp burden, and not a disease specific measure of fungal invasion. So, the endoscopic findings needs to be interpreted together with clinical, radiological and where indicated histological features.

The mean Lund–Mackay score was reduced by 10.7 points or roughly 64.8% of the mean baseline score. This was a large descriptive reduction, and was similar to the radiological improvement seen in other studies.⁸ However, due to this lack of paired participant-level data, a paired confidence interval, test statistic or standardized effect size could not be calculated. In addition, anatomic changes can occur following surgery which can greatly influence the Lund–Mackay score, and the score was created to estimate opacification of sinuses and not the presence of invasive fungal disease. Therefore, it is important to note that the radiological findings should not be the sole criterion of disease clearance.

The 2-month voriconazole therapy was well tolerated. The overall reduced rates of adverse effected in the current trial compared to some previously reported series may be due to shorter treatment courses and exclusion of patients with severe hepatic and renal impairment.¹³ The results thus confirm the short-term tolerability in the selected patient population, but do not confirm the long-term safety profile of treatment in patients with advanced systemic disease.

No statistically significant association was identified between short-term disease control and gender, age, group, or residence. Participants presenting within eight weeks had a higher observed disease-control proportion than those presenting later, but the association was statistically inconclusive after exact testing. This pattern may still be clinically relevant because delayed presentation can permit greater tissue invasion, higher fungal burden, bony destruction, and extension beyond the sinonasal compartment. Retrospective evidence has similarly suggested that disease extent and delayed recognition influence outcomes in CIFRS.¹⁴ However, the present subgroup analysis was exploratory, included only 12 treatment failures, and was not adjusted for disease severity, immune status, comorbidities, or completeness of surgical debridement.

The results obtained overall were favourable for a selected group of patients who had CIFRS, treated with FESS and oral voriconazole. The results support the potential efficacy of this combination. Further comparative studies with longer follow-up are needed for determining the best antifungal agent, the duration of treatment, and for monitoring for long-term disease control.

CONCLUSION

FESS followed by 2 months course of oral voriconazole demonstrated short-term disease control in 80.0% of patients with chronic invasive fungal rhinosinusitis. High rates of symptom resolution and reductions in radiological and endoscopic disease burden were noted.

Majority of patient (80.0 %) did not experience any adverse effects of therapy.

Limitations of the study: The major limitation of this study was the lack of a control group. Therefore, the findings observed were not directly due to the administration of voriconazole. There was a limited number of patients (60) who were treated at a single center so the results were not generalizable, and patients were excluded from those with orbital or intracranial extension meaning that this was not applicable to more advanced disease. An important limitation is the lack of reporting of fungal species, immune status, and voriconazole serum levels as well as degree of debridement to evaluate important prognostic and pharmacological parameters. The Lildholdt scale was an indirect measure of disease activity and the radiological analysis did not include paired inferential statistics. The 12 week period of follow up was also inadequate for the evaluation of late recurrence, cumulative toxicity and long term side effects of voriconazole.

ETHICAL APPROVAL

Ethical approval of article was granted by the Ethics Review Committee Fatima Jinnah Medical University, Lahore

AUTHOR'S CONTRIBUTIONS

MS, BA, MA, SN: Conceived idea, design, manuscript writing, data collection, data analysis

WJ: Manuscript writing, proof reading

AW: Manuscript writing, statistical analysis

All Authors: Approval of the final version of the manuscript to be published

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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