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Comparison of fluconazole and itraconazole for treatment of rhinomaxillary mucormycosis

Rhinomaxiler mukorikozis tedavisinde flukonazol ve itrakonazolun karşılaştırılması

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Abstract

Aim: Rhinomaxillary mucormycosis (RMM) is a detrimental and progressive deep fungal infection which predominantly affects immunocompromised patients. The disease has heterogeneity in clinical manifestation and presents with unfavorable consequences. Despite recent advances in the diagnosis and treatment, the disease has inadequate prognosis overall. The aim of our study is to compare Fluconazole vs. Itraconazole for the management of RMM.

Methods: We retrieved demographic, clinical, radiological and histopathological data of patients affected with osteomyelitis in head and neck region and 33 patients exclusively affected with RMM were separated from departmental records. Several characteristics such as Gender, age, Diabetic status, co-morbidity were observed. Patients were randomly distributed in two groups with respect to the azole drug prescribed to them. Group A was given Fluconazole while group B was given Itraconazole. Aggressive surgery with concomitant use of antifungal drug was the mandatory treatment in all patients. Regular monitoring of side effects of drugs and recurrence was carried out for prolonged time.

Results: Overall, 18 patients were male and 15 patients were female with a ratio of M:F 1.2. Mean age of patients was 48.21 (11.66) with the age range from 25 years to 70 years. Out of 33 patients, 30 of the patients (90.9%) were diabetic. Fifteen patients in Group A were managed with Fluconazole while 18 patients in group B were treated with Itraconazole. There was no statistically significant difference observed in most of the clinical signs and symptoms presented in both groups as $P>0.05$ except for bone necrosis ($P=0.381$). In group A, 4 patients exhibited recurrence (26.6%) while in group B, 5 (27.7%) patients presented with recurrence ($P=0.943$).

Conclusion: Aggressive surgical approach along with supportive antifungal medication remained the mainstay of the treatment. Between Fluconazole and Itraconazole there was no difference observed.

Keywords: Rhinomaxillary mucormycosis, Fluconazole, Itraconazole

Öz

Amaç: Rhinomaksiler mukormikoz (RMM), baskın olarak immün sistemi baskılanmış hastaları etkileyen, zararlı ve ilerleyici bir derin fungal enfeksiyondur. Hastalık klinik tezahürde heterojenliğe sahiptir ve olumsuz sonuçlar doğurmaktadır. Çalışmamızın amacı, RMM tedavisi için Fluconazole - Itraconazole uygulamasını karşılaştırmaktır.

Yöntemler: Baş ve boyun bölgesinde osteomiyelit ile etkilenen hastaların demografik, klinik, radyolojik ve histopatolojik verilerini aldık ve sadece RMM'den etkilenen 33 hasta bölümsel kayıtlardan ayrıldı. Cinsiyet, yaş, diyabetik durum, komorbidite gibi çeşitli özellikler kaydedildi. Hastalar, kendilerine verilen azol ilacı açısından rastgele iki gruba ayrıldı. A grubuna Flukonazol, B grubuna Itrakonazol verildi. Antifungal ilacın birlikte kullanılması ile yapılan agresif cerrahi, tüm hastalarda zorunlu tedavi idi. İlaçların yan etkilerinin düzenli olarak izlenmesi ve tekrarlama uzun süre takip edildi.

Bulgular: Toplamda 18 hasta erkek, 15 hasta kadındı (E/K 1,2). Hastaların yaş ortalaması 48.21 (11,66), yaşları 25 ile 70 arasında değişmekteydi. 33 hastanın 30'u (%90,9) diyabetikti. Grup A'da 15 hasta Fluconazole ile tedavi edilirken, grup B'de 18 hasta Itraconazole ile tedavi edildi. Kemik nekrozu dışında her iki grupta da sunulan klinik belirti ve semptomların çoğunda $P>0,05$ düzeyinde istatistiksel olarak anlamlı bir fark bulunmadı ($P=0,381$). Grup A'da 4 hastada nüks görüldü (%26,6), grup B'de ise 5 hastada (%27,7) nüks saptandı ($P=0,943$).

Sonuç: Destekleyici antifungal ilaçlar ile birlikte agresif cerrahi yaklaşım tedavinin dayanak noktası olarak kaldı. Flukonazol ve Itrakonazol arasında anlamlı bir fark gözlenmedi.

Anahtar kelimeler: Rhinomaksiler mukormikoz, Flukonazol, Itrakonazol

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Introduction

Rhinomaxillary mucormycosis (RMM) is an angioinvasive fungal infection with high mortality rate [1]. It is caused by saprophytic filamentous organism, which belongs to the family Mucoraceae, class Phycomycetes of order Mucorale [2,3]. Mucormycosis has wide spectrum of clinical forms as cutaneous, rhinocerebral, rhinomaxillary, pulmonary, gastrointestinal and disseminated fatal infection [4]. However, the majority of the cases affecting the craniofacial region are rhino-orbito-cerebral Mucormycosis having incidence of 30-50% of all reported cases [4,5]. RMM is a fulminating opportunistic infection, particularly documented in immunocompromised patients with diabetes mellitus, neutropenia, malignancy, chronic renal failure and organ transplant patients [6]. However, it is seldom found in HIV positive patients [7]. The most common pathway of spread of RMM is inhalational, thereby affecting sinuses and respiratory tract [7]. Rarely, it has been reported in healthy immunocompetent patients with trauma, burn and surgery with infection spreading through cutaneous pathway [6,8]. Eminent serum level of unbound iron raises probability of mucormycosis because iron is the essential virulence factor for the fungi [9]. RMM originates from nasal or oral mucosa, extends to paranasal sinuses, orbit and cerebrum [10]. Patients with extensive disease present with headache fever, proptosis, sinusitis, ocular pain, vision loss, nasal discharge and palatal eschar [4,5,9]. Reported literature shows age range of 5–65 years with mean age of 39.9 (20.3) years, age range of 18 to 70 years with a mean of 47.3 (14.4) years and mean age of 50.7 (19.9) years. [5,6,9].

Early diagnosis is the crucial factor for prognosis of the disease because of its devastating nature. Clinical examination, Computerized Tomography (CT) scan or Magnetic resonance imaging (MRI) scan facilitates the presumptive diagnosis. Definitive diagnosis requires biopsy for histopathological evidence of aseptate hyphae with branches at right angle [10]. Primary treatment includes aggressive surgical debridement with prompt antifungal drug like amphotericin B, Fluconazole, Itraconazole, Posaconazole or Voriconazole. Additional supportive therapy includes iron chelators, caspofungin and hyperbaric oxygen [11]. Although, the standard antifungal therapy is parenteral infusion of amphotericin B but it has a disadvantage of prolonged hospitalization and need for regular monitoring because of its significant side effects [12]. Injection site allergic reaction requires administration of diphenhydramine [12]. Hence there was a need of alternative medication with minimal side effects and equal efficacy. So in our study we compared the efficacy and safety of fluconazole vs. Itraconazole for management of RMM. Alternative antifungal treatment includes use of azoles, preferentially Posaconazole [13].

Materials and methods

Case files of all the patients diagnosed with mucormycosis from January 2015 to December 2016 were retrieved from the departmental record. History, demographic data, clinical data, radiographical findings, histopathological analysis, treatment given and post-op results were collected. All patients, irrespective of age and gender who were diagnosed clinically, radiologically and histopathologically as having RMM were evaluated in the study. Patient suffering from Mucormycosis of maxillofacial region were included in the study, patients having bone necrosis, osteomyelitis or sinusitis for reasons other than Mucormycosis were excluded from the study.

Clinical diagnosis was completed on the basis of diverse signs and symptoms including necrotic palatal eschar, nasal obstruction, and tooth mobility, proptosis and vision loss. Radiological evidence (Figure 1) represented erosion of maxillary sinus wall, opacification of paranasal sinus, altered air/fluid levels of sinus, necrosis of dentoalveolar segment and extension beyond sinus to orbit. Histopathology on biopsy sample showed broad and irregular non septate hyphae which branches at right angle.

After the confirmation of diagnosis, antifungal medication was started and meanwhile the patient was prepared for surgical debridement. Preoperative antifungal was prescribed prior to surgery and post-operative antifungal was given to patients for 3 months. Patients were randomly allocated into two groups. In Group A, patients were managed with 150 mg fluconazole BD for 1 month and OD for 2 months while patients in Group B were prescribed Itraconazole 100mg BD for 1 month and OD for 2 months. During the treatment and postoperative period, patients were monitored clinically and radiologically for recurrence. Regular blood tests including serum urea and creatinine, electrolytes, liver function tests and renal function tests were conducted at regular intervals to monitor side effects of azole drugs. The results obtained of both groups were compared for efficacy, potency and side effects. All the patients were followed up for evaluation of recurrence. Surgical debridement remained the definite treatment. Rehabilitation in successful cases was carried out with maxillary obturators.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software (IBM SPSS v20.0, IBM Corporation, Armonk, NY, USA) was used to analyze the data. Frequency, percentages, means and standard deviations were calculated for different qualitative and quantitative variables. Patients were divided into two groups with respect to antifungal medication. Variables in both the groups were compared with chi-square test and *P*-value of <0.05 was considered as statistically significant.

Results

A total of 33 individual cases of RMM were analyzed and divided into two groups with reference to antifungal medication provided to them. Group A included 15 patients treated with fluconazole. Group B comprised of 18 patients treated with Itraconazole. Clinical site involved was Maxilla, with 14 (42.4%) of the cases affecting the left maxilla, 12 (36.4%) affecting right maxilla and 7 (21.2%) of the cases were bilateral. Diabetes mellitus (DM) was associated with RMM in 30 of the cases (90.9%) evaluated in our statistical analysis. Out of these, 7 (21.2%) diabetic patients were controlled and 23 (69.7%) had uncontrolled DM (Table 1).

Out of all 33 patients with mucorale infection, 12 patients (36.4%) had co infection of hepatitis. In Group A, 5 were females and 10 were males (M: F 2:1), age range was from

26yr to 65 year with a mean of 42.8 (9.27) years. In Group B, 10 were females and 8 were males (M:F 1:1.25), age range was from 25yr to 70 year with mean age 52.72 (11.19). Generalized symptoms of fever, headache and lethargy were diagnosed in all cases in both groups. Overall, common clinical features were nasal obstruction (93.9%) and midface bone necrosis (87.9%). Out of 33 patients, Palatal eschar was present in 25 patients (75.8%) as shown in Figure 2. Clinical symptoms observed in both groups are shown in Table 2.

There was no statistically significant difference observed in all clinical signs and symptoms presented in both groups as p>0.05 except for bone necrosis (P<0.05). No statistics of Nasal obstruction was calculated because it was a constant clinical feature in both groups.

Surgical debridement combined with the pre-operative and post- operative antifungals was the principal treatment. Fluconazole was given to 15 patients in Group A and Itraconazole was given to 18 patients in Group B. Surgical management and recurrence in both groups is described in table 3.

After maxillectomy (figure 3), patients were monitored for prognosis and success. Maxillary obturators were given to all patients after aggressive surgical approach as shown in figure 4. Overall, 27.27% or 9 cases in both groups exhibited recurrence as shown in table 3. The chi square results of recurrence in both groups illustrated value of P=0.943, hence there was no remarkable difference in the results. RMM was the independent predictor of death with mortality rate of 3%. Mean follow up period was 29.33 (5.69) months.

Table 1: Diabetic status of the patients

Diabetic status	n	%
Absent	3	9.1
Controlled Diabetes	7	21.2
Uncontrolled Diabetes	23	69.7

Table 2: Clinical symptoms of both groups

Clinical symptoms	Group A		Group B		*P*-value
	n	%	n	%	
Proptosis	4	26.67	6	33.3	0.678
Partial Vision Loss	3	20	4	22.2	0.982
Complete vision loss	1	6.67	1	5.5	0.982
Eschar	11	73.3	14	77.7	0.767
Pus discharge	12	80	13	72.2	0.604
Tooth mobility	11	73.3	13	72.2	0.943
Nasal obstruction	15	100	18	100	_
Bone necrosis	14	93.3	15	83.3	0.381
Nerve Involvement	5	33.3	6	33.3	1.0

Table 3: Surgical management and recurrence in both groups

	Group A		Group B	
	n	%	n	%
Partial maxillectomy	10	66.6	11	61.1
Total maxillectomy without involving orbit	2	13.3	3	16.6
Total maxillectomy with involving orbit	3	20	4	22.2
Recurrence	4	26.6	5	27.7

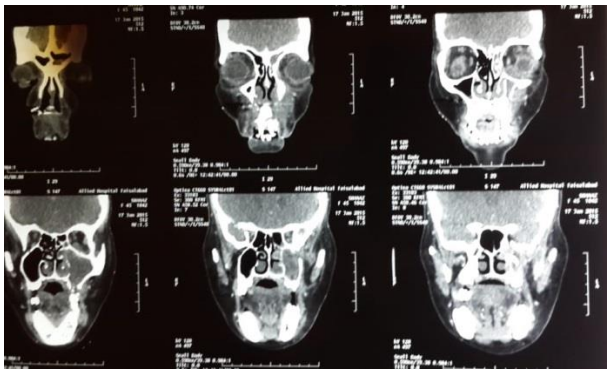

Figure 1: Computed tomography scan showing involvement of left maxillary sinus and nasal cavity

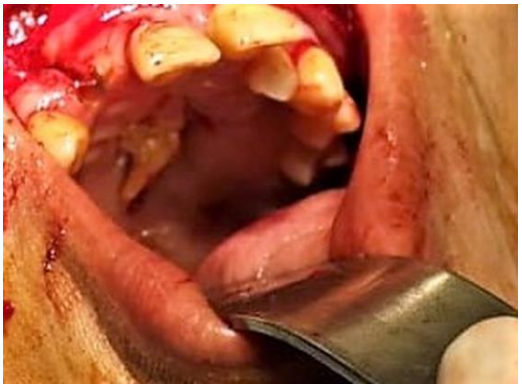

Figure 2: Palatal necrosis/eschar in a patient affected with rhinomaxillary mucormycosis

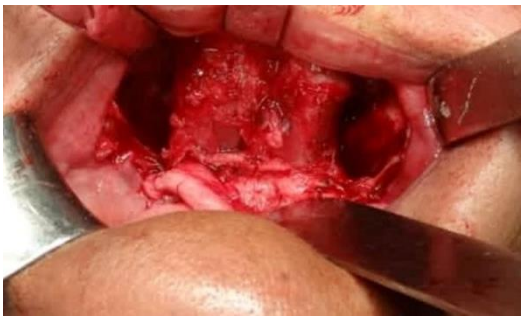

Figure 3: Intraoral photograph of total maxillectomy

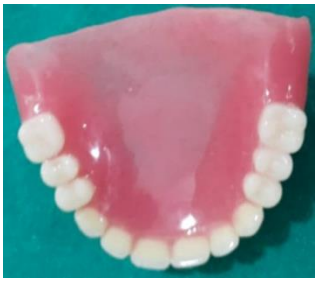

Figure 4: Maxillary Obturator for the patient after total maxillectomy

Discussion

RMM is an aggressive fungal disease with threatening consequences. It is non-contagious infection of nose, maxilla, sinuses and orbit which spreads through inhalational spongiospores in air or via direct mucosal contact in susceptible individuals [5]. It extends from paranasal sinuses and rapidly progress to involve orbit causing proptosis, vision impairment and blindness [14,15]. This retrospective study enabled assessment of RMM cases in terms of clinical signs, management, recurrence and fatality. Patients were distributed in two groups with respect to antifungal medication given to them for 3 months.

In our study, 18 out of 33 patients were male (54.5%), while 15 patients were female (45.4%), with ratio of M: F 1.2:1. This data is comparable to clinical study done by Carlos et al [5]. Notably in our study, 30 out 33 patients (90.9%) had diabetes as a predisposing factor. This strong correlation between RMM and Diabetes mellitus in our study is similar to data collected in different series [16-18]. Majority of the patients had uncontrolled diabetes but with the help of medical practitioners the blood sugar level of patients was brought under control by placing them on insulin. Diabetic ketoacidosis is a significant risk factor because fungi produces ketoreductase enzyme to utilize ketone bodies for growth [19].

Clinically, all affected patients presented with fever, headache and sinusitis. Overall, in both groups common signs

and symptoms observed were eschar formation (75.8%), pus discharge (75.8%), tooth mobility (72.7%), nasal obstruction (100%) and bone necrosis (87.9%). The most adverse clinical feature was complete vision loss reported in 2 patients (6.1%). In our study, Intranasal and palatal eschar was the most frequent finding (75.9%) as compared to a retrospective study which mentions incidence of 40-50% only [16].

Essential aids for the management of disease included detailed history, clinical and cranial nerve examination, CT scans, blood tests and biopsy of the lesion. Acknowledged treatment measures consist of aggressive surgical debridement and antifungal medication like amphotericin B, Fluconazole, Itraconazole, Posaconazole and Voriconazole. In our study treatment regimen consisted only of Fluconazole and Itraconazole for 3 months. Group A received Zolanix (fluconazole) 150mg BD for one month, followed by OD dose for two months. Group B was administered Itraconazole (ICON) 100mg BD for one month, followed by OD dose for two months. A total expense of 3 month regimen for fluconazole was PKR 11,970 ($103.54) and total cost of ICON 3 month regimen was PKR 6,150 ($53.20). During the treatment, Patients were monitored for liver function tests, renal function tests, urea and creatinine and blood electrolytes.

Common side effects of azoles include abdominal distress, headache and pruritus. Generally, amphotericin drug is preferred in terms of efficacy but there are certain limitations because of its potential side effects [21]. Caitlin et al emphasize on the improved efficacy of amphotericin in combination with caspofungin, compared to monotherapy [22]. There is increased risk of nephrotoxicity in patients managed with amphotericin for long term, hence there is need for regular renal function assessment and monitoring for hypokalemia, hypomagnesaemia and metabolic acidosis [23,24]. Its proven nephrotoxicity may require withdrawal of the treatment despite fatal fungal infection [24]. Atahan et al. [25] mentions prolonged duration of 6 months treatment with amphotericin followed by oral fluconazole. Furthermore patient requires hospital administration and parenteral infusion at dose of amphotericin 1-1.5 mg per kg because of limited GIT absorption and bioavailability [26]. In addition to this amphotericin infusion is associated with injection site irritation, swelling and pain. It is also known to cause tachypnea 1-3 hours after infusion.

On the contrary, azoles have sufficient oral bioavailability therefore it can safely be administered orally. Fluconazole has >90% bioavailability and Itraconazole has 55% bioavailability [27]. Since no parenteral injection is required; it is advantageous with regard to patient comfort. Furthermore, azoles are not strongly correlated with deranged renal function tests and raised urea and creatinine as compared to nephrotoxic amphotericin. Another benefit of Fluconazole is its availability in IV formulation as well for patients who are unable to take oral medication. In our study, none of the patients presented with side effects severe enough warranting withdrawal of the drug. However, Itraconazole is associated with weight gain [28]. Posaconazole and voriconazole were not included in our management plan because of lack of availability in our setup and high cost. In addition to this, deferasirox iron chelating agent is considered as salvage therapy for progressive mucormycosis [29]. However it was not used in our study.

Overall, there was no significant difference observed in potency, efficacy and safety in both groups. The azoles were used preoperatively and post operatively with intensive surgical debridement of devitalized tissue in all patients. Aggressive surgical management remained the mainstay of treatment required to eradicate the fungus affected necrotic tissue. All patients were kept on follow up and recurrence was addressed immediately. There were total of 9 cases of recurrence of which 4 belonged to Group A and 5 were in Group B. One patient in group 2 succumbed to disease after recurrence. Maxillary obturators were used as permanent rehabilitation option because uncontrolled diabetes is a poor indicator for successful bone grafting and implants.

Insignificant results were obtained owing to a relatively small sample size. Future studies with a larger population are recommended in order to achieve significant results.

Conclusion

RMM is the debilitating fungal infection which requires surgical approach and early medical intervention to improve the prognosis. Immunocompromised patients, particularly uncontrolled diabetics impose the significant risk in acquiring the disease. In our study, Fluconazole and Itraconazole showed no differences in recurrence and presentation of clinical signs and symptoms except for the bone necrosis. Therefore, the extensive surgical debridement is the mainstay of the treatment with adjunctive treatment with antifungal medications.

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