The Role of Systemic Antifungal Drugs as an Adjuvant to Surgical Treatment of Fungal Sinusitis

Systematic Review

Submitted for the Partial fulfillment of Master Degree in Otorhinolaryngology

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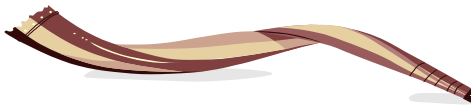

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Introduction

Fungal rhinosinusitis is divided according to histopathological evidence of tissue invasion by fungi into: fulminant, chronic invasive, granulomatous invasive, eosinophilic, and mycetoma or aspergilloma of the paranasal sinus **(Adelson et al., 2005).**

There are different lines of treatment for fungal rhinosinusitis according to the clinical presentation and the histopathological finding. However the treatment of choice for all types of fungal sinusitis is surgical. Medical treatment depends on the type of infection and the presence of invasion **(Pagella et al., 2007).**

The combination of endonasal surgical debridement and systemic antifungal drugs is considered by most surgeons as the best line of treatment of fulminant fungal rhinosinusitis, chronic invasive fungal rhinosinusitis and granulomatous invasive rhinosinusitis. Open surgery should be preferred in the presence of intraorbital extension, palatal and/or intracerebral involvement **(Sirdhara et al., 2005).**

Sinus surgery is the main treatment for patients with invasive fungal rhinosinusitis and liposomal amphotericin B is an effective adjuvant medical treatment. However, the degree of immunosuppression of the patients, the extension of fungal

rhinosinusitis and perhaps the species of fungus are important factors determining the clinical response **(Sungkanuparph et al., 2001).**

Mc Ginnis et al (1997) found that systemic antifungal drugs as Voriconazole (second generation triazole systemic antifungal drug) has fewer side effects observed in the form of transient visual disturbance in **(30%**) of the patients with invasive sinus aspergillosis, hepatotoxicity in (**10%**) of the patients, and rash in (**5%**) of the patients.

Groll et al (1998) found that liposomal amphotericin B had higher therapeutic effect, reduced nephrotoxicity, rare drug resistance, and well tolerated than conventional amphotericin B.

Reversing the underlying disease and immunosuppression was as important as the surgical and systemic antifungal treatment of invasive fungal rhinosinusitis **(Spellberg et al., 2009).**

Although controversy still exists, recent evidence supports that eosinophilic fungal rhinosinusitis is an immunologic rather than infectious disease process, so that the current treatment of eosinophilic fungal rhinosinusitis consists of a combination of surgery and corticosteroid therapy without the need of systemic antifungal drugs **(Marple et al., 2000).**

Surgical removal of the fungal mass is the treatment of choice in all cases of sinus mycetoma (aspergilloma) without needing for systemic antifungal therapy **(Grosjean et al., 2007).**

Aim of the Work

Systematic review of the English language literature to evaluate if the systemic antifungal drugs are effective adjuvant to surgical treatment in the management of fungal rhinosinusitis or not.

Material and Methods

This study utilized systematic reviewing to evaluate if the systemic antifungal drugs are effective adjuvant to surgical treatment in the management of fungal rhinosinusitis or not.

To fulfill the criteria of systematic review in this study the following steps were followed:

1- Determination of the target question:

Is there a role of systemic antifungal drugs in the treatment of fungal rhinosinusitis?

2- Identification and location of articles:

Searching of the pub-med (Medline-data base) by the following key words:

- Fungal sinusitis treatment.
- Systemic antifungal drugs compared with other treatment modalities of fungal sinusitis.
- Systemic antifungal drugs and fungal sinusitis.

Limits of the search: the search was limited to articles published in English language and human studies, and limited in the last 25 years.

3- Screening and evaluations:

The articles included were screened to report on the outcome of response to the treatment and effectivity of systemic antifungal drugs adjuvant to surgical treatment of fungal rhinosinusitis.

Details of our search:

1- search of the key word "fungal sinusitis treatment":

The search yielded **2543** abstracts and articles till August **2011**.

2- search using keyword "systemic antifungal drugs, fungal sinusitis":

The search yieldes **69** abstract and articles till August **2011**.

The Different Pathological Types of Fungal Rhinosinusitis:

Categorization of fungal rhinosinusitis is based on histopathological finding, and can be broadly divided to two categories: invasive and non-invasive according to invasion of mucosal layers. Three types of fungal rhinosinusitis are tissue invasive infectious disease: Acute necrotizing (fulminant), chronic invasive, and granulomatous invasive. Two non-invasive fungal rhinosinusitis disorders are fungal ball (sinus mycetoma) and allergic fungal rhinosinusitis **(Thrasher et al., 2003).**

Charkrabarti et al (2004) identified different species of fungi like Aspergillus (most common causative organism), Histoplasma Capsulatum, and Sporothrix fungus which is isolated from patients with allergic fungal rhinosinusitis and also Bipolaris which was isolated from affected sinus tissues.

Regarding host factor, it is well known that fulminant fungal rhinosinusitis is common in immunocompromised host, especially patients with bone marrow transplantation, acquired immunodeficiency disease syndrome, uncontrolled diabetes mellitus, malignant diseases such as, leukaemia and lymphoma **(Charakrabarti et al., 2000).**

Borish et al (2006) suggested that the pathogenesis of allergic fungal rhinosinusitis was due to release of immunoglobulin E and immunoglobulin A in response to trapped fungal antigen in the sinus mucosa.

Diagnosis of fungal rhinosinusitis should be considered in patient with chronic sinusitis especially associated with intractable symptoms despite administration of adequate treatment. Direct microscopical examination, culture and histopathology of the cheesy material (obtained from the affected sinus help in early diagnosis of the aetiology. The hematoxylin and eosin histologic staining of surgical sinus specimens shows characteristic features of allergic fungal rhinosinusitis **(Figure 1).** The mucosa appears hypertrophic and hyperplastic. It exhibits a dense inflammatory infiltrate of plasma cells, small lymphocytes, eosinophils and mucus plugs composed of strongly masses of degenerating eosinophils staining thick laminated sheets "eosinophil concretions". Presence of Charcot-Leyden (lysophospholipase) crystal microscopically **(Saravanan et al., 2006).**

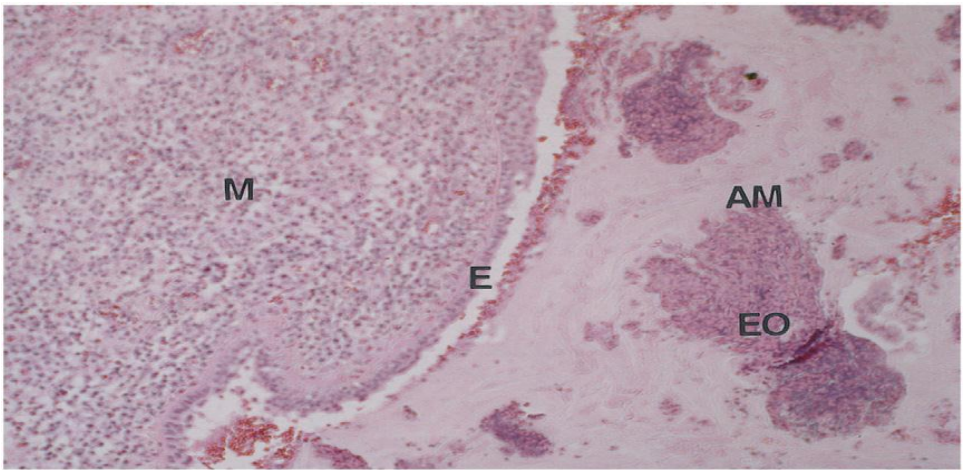

Figure (1): Surgical sinus histopathology from a representative patient with allergic fungal rhinosinusitis (hematoxylin and eosin stain). **(M)** sinus mucosa, **(E)** epithelium, **(AM)** allergic mucin, **(EO)** masses of numerous eosinophils 'eosinophil concretions' **(Schubert et al., 1998).**

Radiology plays important role in diagnosis of fungal rhinosinusitis. Computed tomography scan is the best choice for diagnosis of bone erosion and heterogenous opacity in acute and chronic diseases of the paranasal sinus. Magnetic resonance imaging is superior to computed tomography in differentiating inflammatory from neoplastic diseases and diagnosing the intracranial extension **(Mafee et al., 2006).**

Systemic Antifungal Drugs:

In general the systemic antifungal drugs for the treatment of fungal rhinosinusitis are classified into the following groups: Amphotericin B, Triazoles (itraconazole and voriconazole) and Echinocandins.

A. Amphotericin B is a polyene agent available in four formulation (deoxycholate Amphotericin **B**, Amphotericin **B** colloidal, Amphotericin **B** lipid complex, and liposomal Amphotericin **B**) All act by binding to primary fungal cell membrane sterol and resulting in disruption of osmotic integrity of the membrane with leakage of intracellular potassium, magnesium, sugars, and metabolites, then cellular death **(Beatriz et al., 2000).**

Up to (**50%**) of the patients have adverse reaction to amphotericin B in the form of fever with or without rigor, headache, nausea, and vomiting. Hypotension and anaphlaxis are rare. Nephrotoxicity occurs in up to (**80%**) of the patients and manifested by electrolyte wasting, and distal renal tubular acidosis. It is usually reversible after cessation of the drugs. The dose of amphotericin B may be reduced after a careful assessment of the risk versus benefit to the patient. Thrombophlebitis, normochromic normocytic anaemia, neutropenia, and thrombocytopenia are associated infrequently with amphotericin B therapy. Intensive monitoring of blood urea nitrogen, serum creatinine, potassium, sodium, and magnesium should be done twice weekly, while complete blood count done once weekly **(Deshazo et al., 1998).**

Groll et al (1998) found that liposomal amphotericin B has higher therapeutic effects, reduced nephrotoxicity, rare drug resistance, and well tolerated than conventional amphotericin B.

The usual dose of Amphotericin B is (**0.25- 1** mg/kg/day). Maximum dose is (**1.2** mg/kg/day) in adult and (**1.5** mg/kg/day) in children. Total cumulation dose is (**4-6** gm) in case of intracranial extension. Prior to starting treatment, a test dose of **1** mg of amphotericin B in **50** ml of **5%** glucose is usually infused over **20** minutes in order to assess immediate adverse effects. Vital signs are monitored every fifteen minutes for an hour, and if no serious adverse effects occur, the remainder of the desired dose is adminsterd over **2-6** hours and if tolerated, infusion time may be reduced to two hours **(Rapp et al., 1998).**

B. Triazole group acting by inhibiting the cytochrome **p450** a-denethylase enzyme. This enzyme is involved in the sterol biosynthesis pathway, and this inhibition leads to accumulation of lanosterol, that in turn results in destruction of the fungal cell wall **(Rarrel et al., 1999).**

There were fewer side effects with administration of Azole group in the form of gastrointestinal tract upset, mild elevation of liver enzymes in ***(7%)*** of the patients, rash, headache, alopecia, hypertension, hpokalaemia, and teratogenicity **(Kauffman et al., 1997).**