

Combination Versus Monotherapy for the Treatment of HIV Associated Cryptococcal Meningitis

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ABSTRACT

Objective: To study the efficacy of anti Cryptococcal treatment by cerebrospinal fluid (CSF) fungal negativity after two weeks of treatment with amphotericin B alone or combined with fluconazole in treatment of HIV associated Cryptococcal meningitis (CM).

Materials and Methods: A total of 84 human immunodeficiency virus (HIV) associated CM patients confirmed by CSF culture positivity were recruited for the study. Patients were randomly divided into two groups. Group A was given amphotericin B alone whereas Amphotericin B in combination with fluconazole was given in group B for the treatment of CM. Patients were followed for 14 days.

Results: Maximum number of patients was in the age group 21-49 y. All the 84 patients had <100 CD4 counts/ μ l. After 14 days of the treatment in group A and B, there was no significant difference in terms of fever, headache and neck stiffness as a clinical outcome. But in group B there was improved in altered sensorium and focal neurological deficit as compared to group A. After 14 days of the treatment CSF culture negativity was more in group B as compared to group A.

Conclusion: Amphotericin B in combination with fluconazole is recommended for the treatment of HIV associated CM.

Keywords: Amphotericin B, Combination therapy, Cryptococcal Meningitis, Fluconazole, HIV

INTRODUCTION

Among the opportunistic infections associated with HIV infection CM is the leading one [1]. Park et al., estimated that over one million people worldwide are affected with HIV associated CM [1]. Standard treatment of CM consists of three phases: induction, consolidation, and maintenance. Induction therapy include the use of potent fungicidal drugs and rate of fungal clearance from the cerebral spinal fluid (CSF) during the first two weeks, predicts 10 wk survival, and CSF sterilization by 14 days predicts long-term prognosis [2-4]. Various drug trials have been performed in past for the induction therapy using single drug or in combinations. The use of each drug alone would require higher dosage which would be more toxic to the patients. The combination of drugs usually requires lower doses. This reduction in dosage decreases the toxicity by drug, which results in a higher tolerance to the antifungal by the patient. Current recommended therapy for CM consists of two weeks of amphotericin B in combination with flucytosine [5,6]. However, flucytosine is frequently unavailable in most of the disease endemic areas and has high cost and side effects making it less useful in low economic areas. Fluconazole which is a selective inhibitor of fungal cytochrome p 450, has low rates of adverse events. Despite of readily penetration into CSF, it is associated with poor outcomes when used as alone for CM [5]. However, Fluconazole in combination with amphotericin B shows similar results as that of amphotericin B plus flucytosine [7,8]. WHO suggested it as an alternative to flucytosine for combination therapy with amphotericin B [5].

Different studies have been conducted regarding the dosage and efficacy of combination therapy of fluconazole with amphotericin B. Brouwer et al., in their study uses amphotericin B at a dose of 0.7 mg per kg per day and fluconazole at a dose of 400 mg per day and shows no improvement in the rate of fungal clearance from the CSF [2]. In contrast, other authors shows that increased doses of amphotericin B (1 mg per kilogram per day) and fluconazole (800 to 1200 mg per day) independently results in improved fungal clearance [3,7].

Given these considerations we conducted a study that compared the clinical improvement and CSF fungal culture negativity of amphotericin alone or in combination with fluconazole (400 mg or 6 mg/kg) daily doses for induction treatment of newly diagnosed CM among HIV infected patients.

MATERIALS AND METHODS

The randomized control study was conducted at Department of Medicine, Sri Aurobindo Medical College and PG Institute during Oct 2012 to Sep 2014 and comprised of 84 cases the age group of >12 years old admitted with HIV infection having CM diagnosed by CSF study. Patients with meningitis due to tubercular, toxoplasmosis, histoplasmosis and bacterial meningitis were excluded from the study.

CM was defined as clinical features of meningitis/meningoencephalitis along with positive CSF Cryptococcal antigen test or isolation of *Cryptococcus neoformans* in the CSF culture.

CSF culture positive samples were randomized into two groups. Injection Amphotericin B (0.7-1 mg/kg/day) alone was given Group A while Amphotericin B (0.7-1 mg/kg/day) along with fluconazole was given in group B for 14 days.

Patient's details such as age, sex clinical symptoms at presentation, past history of treatment, duration of treatment etc. were recorded.

STATISTICAL ANALYSIS

The statistical analysis was done on SPSS 20.0. Quantitative data were analysed by using student t-test for independent sample and paired sample t-test for dependent samples. Chi-Square test was used to see difference in frequency of discrete variables among two groups. Mc-Nemar test was applied for paired samples.

RESULTS

A total of 84 patients have been diagnosed with HIV associated CM. The main presenting symptom was headache (83.3%) and fever (90.5%). Neck stiffness was observed in 50 (59.2%) patients

and altered sensorium was observed in 34 (40.5%) of the patients. Fourteen patients had focal neurological deficit at the time of admission. The mean age of patients was approximately same in both the groups (36.8±2.3 y in group A and 35.2±5.3 y in group B). There was also no significant distribution in male to female ratio in between the groups. A total of 78 patients were on Antiretroviral Therapy (ART) of which 38 were in Group A and 40 were from group B. Duration of ART was also similar in both the groups. Before the start of treatment there was no significant difference in CD4 counts, CSF Protein Sugar, Lymphocyte count in two groups [Table/Fig-1]. Culture test for *cryptococcal neoformans* was positive in all the samples before the start of treatment.

After the 14 days of the treatment we observed there was significant reduction in fever, headache, neck stiffness, altered sensorium, and focal neurological deficit in both the groups. We compared the efficacy of amphotericin B alone and amphotericin B along with fluconazole after 14 days of the treatment, we observed that there was no significant difference in symptoms in respect to fever, headache and neck stiffness [Table/Fig-2]. However, the altered sensorium and focal neurological deficit was markedly reduced in group B as compared to group A. CSF culture positivity was significant reduced in group B as compared to group A.

DISCUSSION

In present study a total of 84 patients having HIV associated CM were enrolled. The most of the patients were in the age group 21-49

Parameter	Group A	Group B	Total	p-value
Age	36.8±2.3 year	35.2±5.3 year	36.0±3.8	0.0764
Sex (Male: Female)	35:7	32:10	67:17	0.5880
CSF Protein	62.23±25.13	58.1±24.81	60.2±24.9	0.4506
CSF Sugar	43.42±12.08	42.11±12.21	42.8±12.1	0.6224
CSF Lymphocyte	42.19±37.69	46.19±37.37	44.19±37.2	0.6266
CD4 Cells	43.54±31.9	51.21±27.81	47.8±29.8	0.2436
Fever	36(85.7)	38(90.5)	74(90.2)	0.7379
Headache	36(85.7)	34(80.9)	70(83.3)	0.7707
Vomiting	34(80.9)	35(83.3)	69(82.1)	0.7757
Altered Sensorium	18(42.9)	16(38.1)	34(40.1)	0.8241
Neck Stiffness	24(57.1)	26(61.9)	50(59.2)	0.8241
Focal neuronal Deficit	8(19)	6(14.3)	14(16.6)	0.7697

[Table/Fig-1]: Baseline clinical pathological profile in two groups

BCC subtype	Group A			Group B		
	baseline	At 14 days	p-value	Baseline	At 14 days	p-value
Fever	36(85.7)	12(28.6)	<0.0001	38(90.5)	10(23.81)	<0.0001
Headache	36(85.7)	18(42.9)	<0.0001	34(80.9)	14(33.3)	<0.0001
Vomiting	34(80.9)	16(38.1)	<0.0001	35(83.3)	13(30.9)	<0.0001
Altered Sensorium	18(42.9)	6(14.29)	<0.0001	16(38.1)	1(2.38)	<0.0001
Neck Stiffness	24(57.1)	10(23.8)	<0.0001	26(61.9)	10(23.8)	<0.0001
Focal neuronal Deficit	8(19.0)	8(19.0)	1.000	6(14.3)	2(4.8)	<0.0001
Culture positive	42(100)	25(59.5)	<0.0001	42(100)	16(38.1)	<0.0001

[Table/Fig-2]: Clinical symptoms in two groups at baseline and after 14 days of the treatment

y. This is in concordance with the technical report providing national level statistics published by National AIDS Control Organization (NACO) in the year 2012 [9].

Headache and fever were predominant symptoms which is similar to the earlier reports in the literature [10-13]. Altered sensorium was observed in 40.5% of patients in present study. Previous reports

show the 13-73% of altered sensorium in their patients [12-16]. Focal neurological deficit was observed in small number of patients which is also in concordance with previous reports [12-14].

Untreated CM is lethal. A standard of care for the treatment of CM in HIV patients established by a large randomized controlled trial as a combination of amphotericin-B deoxycholate (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) [4]. However, due to high cost and unavailability of flucytosine in many countries; fluconazole may be chosen as second line of therapy in combination with amphotericin B. Yao et al., [8] recently conducted a meta-analysis and concluded that there was no significant difference in terms of survival rate between Amphotericin B in combination with high-dose fluconazole and Amphotericin B in combination with flucytosine. Day et al., [17] in their study also did not found any significant difference in survival between patients receiving amphotericin combined with high-dose fluconazole and those receiving amphotericin B monotherapy.

The rate of decline of CSF yeast counts is a potential marker of survival in the evaluation of antifungal-treatment regimens. In present study, we also found the amphotericin B plus fluconazole is more effective than amphotericin B alone in eradicating the *Cryptococcus neoformans* from CSF in 14 days. A recent study from South Africa did not show a significant difference in rates of CSF yeast clearance between amphotericin B plus flucytosine and amphotericin B plus fluconazole, but the study was limited by its small size and the lower fungal burden in the patients [18]. Another study shows that flucytosine combined with amphotericin B resulted in faster CSF yeast clearance than did amphotericin B monotherapy or amphotericin B plus fluconazole at a daily dose of 400 mg [2]. However, fluconazole is more rapidly fungicidal when administered at a dosage of 1200 mg per day than when administered at a dosage of 800 mg per day [19]. High-dose fluconazole was well tolerated with no adverse liver function abnormalities, in keeping with previous clinical trial data.

Small sample size and shorter follow up period were the limitations to our study. Long term follow-up may be desirable to draw other significant difference between two treatment categories.

CONCLUSION

The amphotericin B with fluconazole therapy for CM improves morbidity in short term and thereby can reduce the cost and complication of prolonged bed ridden state extended immobilization and hospital stay without any additional side effect associated with combination therapy.

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