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Effect of rifampin with bio-enhancer in the treatment of newly diagnosed sputum positive pulmonary tuberculosis patients: A double-center study

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ABSTRACT

Objective: To compare a fixed-dose combination (FDC) of Rifampicin 450 mg, Isoniazid 300 mg, Pyrazinamide 1500 mg and Ethambutol 800 mg (usual care group) and regimen of Rifampicin 200 mg, Isoniazid 300 mg and piperine 10 mg along with Pyrazinamide 1500 mg and Ethambutol 800 mg (intervention care group).
Methods: A randomized, prospective, parallel group study was conducted on newly diagnosed tuberculosis patients. The drugs were given during intensive and continuous phase of treatment to newly diagnosed sputum positive pulmonary tuberculosis. All the patients were subjected to sputum examination, biochemical investigations followed by adverse drug event (ADE) monitoring.
Results: A total of 63 patients completed the study. No significant difference was observed in baseline characteristics of patients between the study groups. At the end of the continuous phase, both the groups showed zero bacteria detection. However, in the intervention group, the rate of sputum conversion was much faster than the usual care group. The rate of increase in SGOT and SGPT was much higher in the usual care group ($p < 0.0001$) than the interventional group ($p < 0.05$). Urea and creatinine has also increased from pre-treatment to end visit. The number of patients reported ADEs was less in the intervention care group (22.22%) when compared to the usual care group (36.84%).
Conclusion: Rifampicin 200 mg with piperine 10 mg FDC is compatible with the usual CAT-1 regimen.

1. Introduction

Tuberculosis (TB) is a contagious lung disease affecting 40% Indian population and about 10% will develop active TB during their lifetime. In 2013, it is appraised 9 million people globally develops TB [1]. World Health Organization (WHO) recommends Directly Observed Treatment Short – Course (DOTS) therapy for control of TB. Standard DOTS Category I drugs comprise Isoniazid, Rifampicin, Ethambutol and Pyrazinamide [2]. Poor medication adherence to the treatment regimen is a major cause of treatment failure and of the emergence of drug-resistant TB. The major factors for non-adherence to TB treatment are long term duration of therapy and adverse effects of the drugs etc.

Recent data show that current pharmacotherapy for TB is inadequate to achieve therapeutic drug serum levels [3,4]. Therefore, there is a necessity to identify a new molecule for the control of TB. The fixed drug combination (FDC) of Rifampicin, Piperine and Isoniazid is available for the treatment of tuberculosis. By adding Piperine, the dose of rifampicin is reduced to 200 mg which possesses to achieve the therapeutic serum level of Rifampicin as of 450 mg [5]. Since the dose of Rifampicin is reduced and the toxicity of Rifampicin is also reduced and thereby better patient compliance is expected. Thus, defaulter rate and development of drug resistance can be reduced. Many studies have considered this point and evaluated the relationship of Piperine and Rifampicin. However, limited data are available in clinical practice [6–8]. The present study was undertaken to find out the superiority of piperine included FDC in TB management.

2. Methods

2.1. Study design

The study was designed as a randomized, prospective, open-label,

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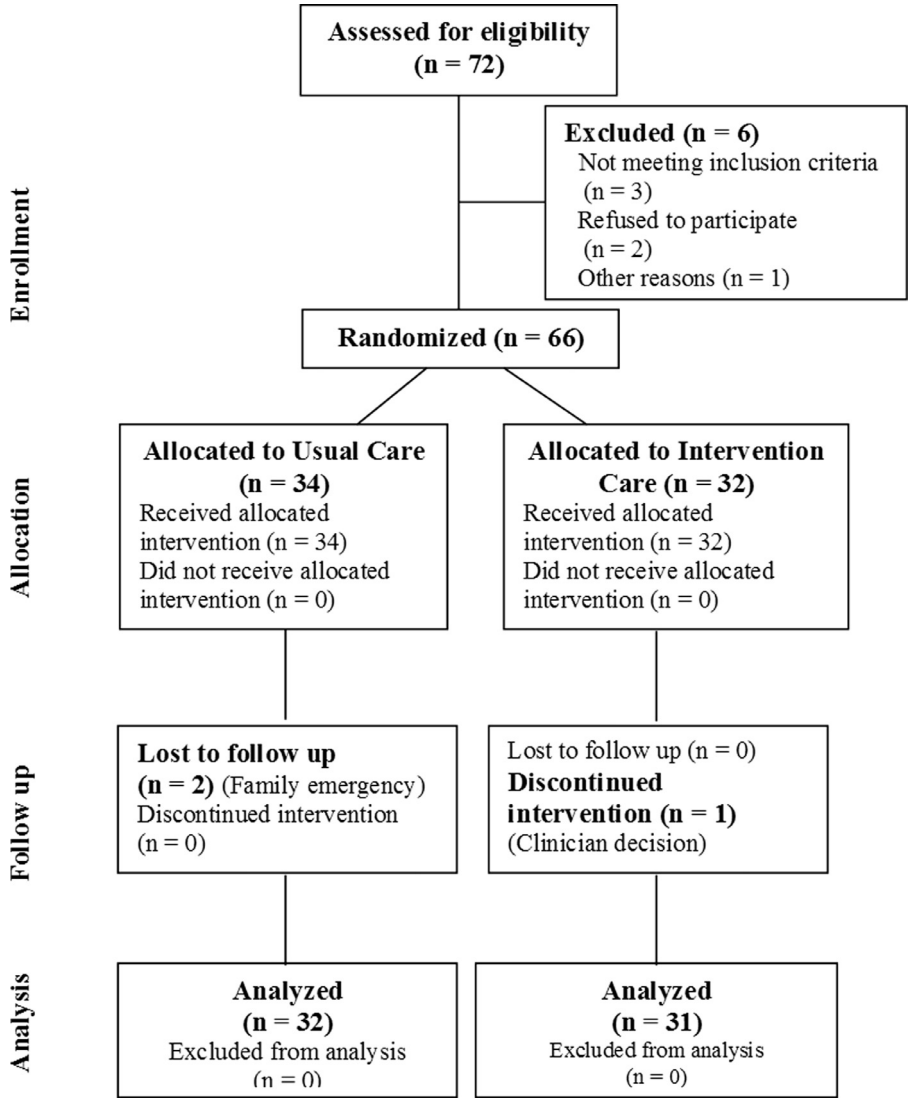

Fig. 1. CONSORT diagram for flow of patients.

parallel group study. Human Institutional Ethics Committee approval was obtained prior to the commencement of the study (481/IEC/2013) and the study was registered in the Clinical Trial Registry – India (CTRI/2015/01/005475). The study was conducted in two centers (1) Department of Pulmonary Medicine, SRM Medical College Hospital and Research Center, Kattankulathur, Kanchipuram district, (2) Government Hospital – Kanchipuram, Thiruvallur district, Tamil Nadu, India.

2.2. Study criteria

Patients were aged between 18 and 60 years, either gender, without co-morbidities and newly diagnosed sputum positive pulmonary tuberculosis, according to RNTCP guidelines and willing to provide informed and written consent were enrolled for the study. A patient with a history of known cases of pulmonary tuberculosis, extra- pulmonary, severe alcoholic, cardiac disorders, HIV positive, pregnant women and lactating mothers, intolerance to FDC for the treatment of tuberculosis and voluntary withdrawal were excluded from the study.

2.3. Treatments

Patients satisfying above study criteria were enrolled in the study. Clinical information relevant for the study was collected from the patients, health care professionals, necessary records and as well as from patient representatives in few cases. Patients were randomized into two groups, namely Usual Care (UC) and Intervention Care (IC) groups. UC group patients received CAT – I regimen (Rifampicin 450 mg, Isoniazid 300 mg, Pyrazinamide 1500 mg and Ethambutol 800 mg) in intensive phase. Isoniazid 300 mg and Rifampicin 450 mg in the continuous phase. IC group patients received Rifampicin 200 mg, Isoniazid 300 mg and piperine 10 mg along with Pyrazinamide 1500 mg and Ethambutol 800 mg in intensive phase. Isoniazid 300 mg and Rifampicin 200 mg and piperine 10 mg in continuation phase.

2.4. Clinical investigation

Both the group patients were subjected to sputum examination and biochemical investigations. The primary efficacy evaluation was based on assessing sputum conversion. The standard bacteriological assessment was performed by a sputum acid fast bacillus (AFB) test. Ziehl-Neelsen's staining of sputum smear was performed. Grading of slides in AFB microscopy was done according to Revised National Treatment Control Program (RNTCP).

Assessment of liver, kidney functions and adverse drug event monitoring were considered to be the secondary tolerability outcome measures. The tolerability of the liver is very important during the treatment of tuberculosis. Rifampicin is a potent drug and the risk of