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Efficacy of N-Acetylcysteine on Prevention of Antituberculosis Drug-Induced Hepatotoxicity

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Abstract: Drug induced hepatitis due to anti-tuberculosis treatment is an important issue. Studies have shown that drug-induced hepatotoxicity is primarily due to oxidative stress caused by the anti-TB drugs and metabolites. A randomized clinical trial was conducted on 85 new TB patients who were aged 50 years or more. Informed consent was obtained from all patients and Patients were randomized in two groups. In control group (n=42), drug regimen included daily doses of ethambutol, pyrazinamide, isoniazid and rifampicin plus placebo. Patients in trial group (n=43) were treated with anti-TB drugs plus N-Acetyl Cysteine. The patients were followed up for 2 months and quality of life of patients measured by questionnaires of SF-12. Statistical analysis was performed using SPSS (statistical software package ver.16) and P- Values less than 0.05 were considered significant. RESULTS showed that: This research showed demographic and disease characteristics of two groups such as gender, age, type of TB (pulmonary and extra-pulmonary), body mass index, laboratory characteristics of patients at the onset of treatment (CBC, ESR, CRP and liver enzymes) had no significant differences and were nearly the same. During treatment, there were significant differences between the two groups regarding the incidence of hepatitis and elevated liver enzymes. In addition, the clinical course and reduced CRP levels were different between them. Also the trial groups compared with the control group seems to have a better quality of life. CONCLUSION: N-Acetyl Cysteine prevented hepatotoxicity significantly and improved the patients' quality of life. With regard to effect of N-acetylcysteine and also low cost and lack of serious side effects we recommend that it be given with other anti-TB drugs during the first month of treatment.

Key words: Anti-TB Drugs · Hepatitis · N-Acetylcysteine · Quality Of Life

INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* complex species. TB incidence in the world in 2011 was 8.7 million (8.3- 9.0 million), equivalent to 125 cases per 100000 population. The majority of TB cases in 2011 have been reported from Asia (59%), Africa (26%) and less often from Mediterranean (7.7%), European (4.3%) and American (3%) regions [1]. About 28.6% of TB patients who received standard treatment developed one or more Adverse Drug Reactions (ADRs) that may result in increase in health care services and affect the anti-TB treatment pattern. Patients with ADRs were more susceptible to develop unfavorable results of anti-TB. This shows the importance of developing strategies to control ADRs both to improve the quality of life and to treat TB safely. The poor patient compliance is partially as a result of adverse effects, especially hepatotoxicity which are common in the first month of starting treatment of anti-TB drugs. Anti-tuberculosis drug-induced hepatotoxicity can be one of the serious implications of INH, RIF and PZA. The incidence of hepatotoxicity reported varying from 2% to 28% consistent with completely different populations and definitions [2-4]. In Europe, the incidence of hepatotoxicity of antituberculosis drugs has been reported about 5.8% to 18.2% [5]. The pathological process of hepatotoxicity is not well-known, however one

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of the causes of hepatotoxicity is Induction of hepatic enzymes and hydrolysis of drugs and the production of toxic metabolites. In addition, acetylator phenotypes and genetic polymorphisms (glutathione S-transferase M1, cytochrome P450 2E1, class II associated HLA-DQ alleles) Oxidative stress, lipid peroxidation, choline deficiency have causative link with hepatotoxicity [6-10]. Decline of reduced glutathione and the activities of glutathione-dependent antioxidant enzymes (glutathione peroxidase, glutathione-S-transferase, superoxide dismutase) in liver mitochondria are associated with hepatotoxicity [11]. Adjuvant treatment with N-acetylcysteine (NAC) increases glutathione in liver cells and thereupon detoxifying toxic substances, [12,13]. NAC increases nitric oxide and causes vasodilatation. [14-16] and successfully penetrates to the blood brain barrier and increases glutathione in brain and alterations in redox pathways [17,18]. So far no drug has been detected to prevent drug hepatotoxicity except stopping the treatment that could increase morbidity and emergence of resistant strains. This study was designed to determine the effect of NAC in prevention of anti-TB drugs hepatitis and quality of life improvement in Tuberculosis patients.

MATERIALS AND METHODS

In a double blind clinical trial, at central province of Iran from September 2012 to December 2013 a total of 88 Patients with newly diagnosed tuberculosis aged over 50 years candidate for anti-TB treatment were randomly assigned to receive two months of four drugs (ethambutol, PZA, RIF and INH) plus NAC (600 mg orally twice daily for 30 days) and followed by four months with INH and RIF as trial group and anti-TB drugs plus placebo (600mg starch orally twice daily for 30 days) as control group.

At the beginning of treatment, serum alanine transaminase (ALT), aspartate transaminase (AST), direct and total bilirubin, C-Reactive Protein (CRP) Erythrocyte Sedimentation Rate (ESR), Complete Blood Count (CBC) levels were measured. Serum ALT, AST, total bilirubin and CRP were measured every two weeks by the end of the second month of treatment or checked whenever patients had symptoms of hepatitis. Patients with chronic diseases of liver, kidney, heart, or viral hepatitis, HIV+, hypersensitivity to NAC, abnormal serum ALT, AST, or bilirubin levels before anti-TB treatment and patients with major psychological disorders were excluded from the study. According to definition of American Thoracic Society anti-TB drugs induced hepatitis was defined as increased of ALT or AST more than three times the upper limit normal (ULN) with the presence of hepatitis symptoms or increased to five times the ULN in the absence of symptoms and return to normal after withdrawal of all anti-TB drugs [4]. In this study we have evaluated the quality of life by standard SF12-Questionnaire in beginning and the end of 1st month of treatment. This trial was registered with Registration ID of IRCT201205259855N1. In this study, all instructions of ethics Committee of Arak University of Medical Sciences Were considered. With a power of 80% and level of 0.05, the sample size was calculated to be 40 for each group and taking into account 10% dropout, a total of 88 patients were enrolled in two groups of case and control. All data were analysed by SPSS software (ver.16) and statistical Analysis were performed by calculation of mean ± standard deviation, ANOVA (Differences between group means), t-test and Mann Whitney test (differences between baseline and follow-up of all parameters in each group) Chi- square test(comparison of categorical variables) and P- Values less than 0.05 were considered significant.

RESULTS

A total of 88 patients were enrolled, during the study, three patients excluded (one patient due to intolerance of NAC and two patients due to use of vitamins during treatment) thus, there were 42 patients in the control group and 43 patients in trial group were included in the final analysis (Figure 1).

In trial group, 48.8% were male and 52.2% were female and 50% of control group were male or female. The mean age of the trial group was 65.3±8.9 and median was 64 years, in the control group mean age was 65.8 ±8.2 and the median was 65 years. Also the two groups were similar in other characteristics such as gender, age, type of TB (pulmonary and extra-pulmonary), body mass index, laboratory characteristics of patients at the onset of treatment (WBC, Hgb, ESR and CRP) at the beginning of treatment. Baseline patient characteristics and comparison of serum mean level of AST, ALT and CRP in two groups are shown in Table 1 & 2.

The occurrence of hepatitis wasn't observed in the trial group But 14.3% of patients in the control group had hepatitis and Serum AST, ALT and bilirubin levels were raised much significantly in control group.

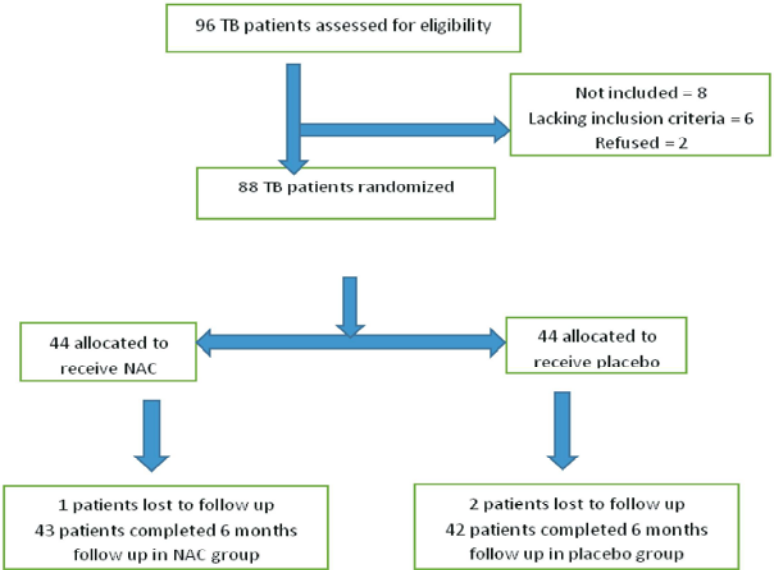

Fig. 1: Flowchart of participants.

Table 1: Comparison of Baseline demographic and disease characteristics in two groups

		Group		
Variable		Trial Group (%)	Control Group (%)	P-Value
BMI	<18.5	20(46.5%)	19(45.2%)	0.9045
	18.5-24.9	17(39.6%)	18(42.9%)	0.7566
	25-29.9	5(11.6%)	4(9.5%)	0.7490
	≥ 30	1(2.3%)	1(2.4%)	0.9840
Pulmonary TB		32(74.4%)	30(71.4%)	0.7566
Extra-pulmonary TB		11(25.6%)	12(28.6%)	
Anemia		22(51.2%)	21(50%)	0.9119
WBC	Leukocyosis	10(23.3%)	12(28.6%)	0.5772
	Leukopenia	5(11.6%)	4(9.5%)	0.7528
ESR↑		34(79.1%)	32(76.2%)	0.7482
Total Bilirobin↑		1(2.3%)	6(14.3%)	0.0444
SF-12score(M±SD)	First Day	27.7±5.9	27.3± 5.7	0.7514
	End of the first month	36.7±7.8	31.8±6.7	0.0026

Table 2: Comparison of AST, ALT and CRP of patients in two groups at intervals of two weeks

Time(Day)	Variable	Trial Group (Mean)	Control Group (Mean)	P-Value
Day 0	AST	29.7±9.7	10.4±31.3	0.4664
	ALT	23.8±13.1	9.3±25.3	0.5434
	CRP	32.7±26.3	33.6±27.2	0.8778
Day 14	AST	37.1±84.5	83.3±128.7	0.0028
	ALT	28.7±81.2	77.3±127.7	0.0006
	CRP	27.1±33.7	28±39.4	0.3454
Day 28	AST	22.9±64.8	52.5±98.2	0.0004
	ALT	35.7±72.5	45.1±101.3	0.0016
	CRP	19.7±21.3	24.6±30.7	0.0564
Day 42	AST	12.8±44.5	32.8±61.7	0.0026
	ALT	15.2±39.7	19.5±51.7	0.0022
	CRP	13.5±15.5	20±26.3	0.0048
Day 56	AST	9.1±31.7	20.4±38.3	0.0610
	ALT	9.5±29.7	11±35.3	0.0146
	CRP	7.5±11.3	13.8±18.3	0.0052

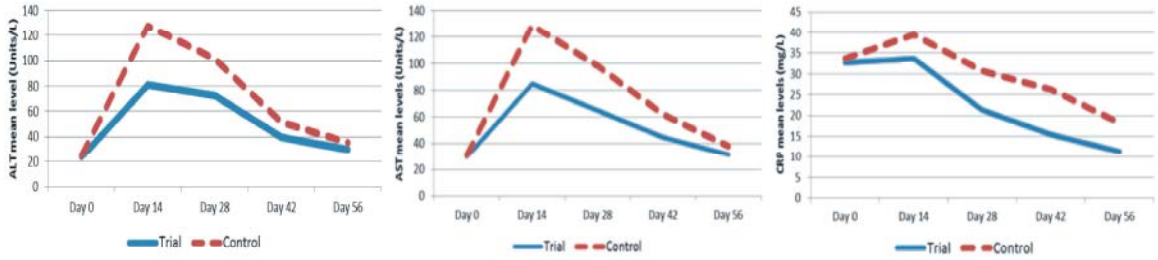

Fig. 2: Trends of AST, ALT & CRP mean levels (units/L) in two groups

Treatment with the NAC reduced the level of enzymes activity (AST, ALT) and the level of total bilirubin. In addition, the clinical course and reduced CRP levels as an important factor in assessing the course of treatment and also the quality of life in trial group seems to have better. Trends of ALT, AST and CRP mean levels in two groups shown in Figures 2.

DISCUSSION

One of the functions of the liver is to remove toxins from the body. It appears that NAC supplementation increases glutathione and plays an important role in the neutralization of toxic substances and has strong protective effect on the cells. This study shows that the two groups in demographic and disease characteristics such as gender, age, type of TB (pulmonary or extra-pulmonary), body mass index, laboratory characteristics of patients at the onset of treatment (such as level of AST or ALT, anemia, increased erythrocyte sedimentation rate and CRP) were not significantly different and were similar. However, between two groups the incidence of hepatitis and elevated liver enzymes following treatment appears to be significantly different. In addition, the clinical course and reduced CRP levels as an important factor in assessing the course of treatment was significantly different. Also the quality of life in trial group compared with the control group seems has been better. The efficacy of the NAC was shown in an animal model in concurrent administration design of anti-TB drugs induced hepatotoxicity [19]. Kranzer *et al*. [20], proved the efficacy and safety of N-acetylcysteine in preventing aminoglycoside-induced ototoxicity as an implications for the treatment of multidrug-resistant TB. Multiple clinical applications of NAC have been explained in literature; Although NAC is known as an antidote to acetaminophen poisoning but there are a variety of clinical applications for NAC, Some studies have shown that NAC has positive effect on the clinical course of COPD, Also, several studies have shown that NAC effective in preventing contrast-induced nephropathy, In addition, NAC significantly relieve the flu in the elderly population, Improved performance of pulmonary function in Idiopathic pulmonary fibrosis and has been effective on Infertility in women with clomiphene-resistant polycystic ovary syndrome. Good evidence from a single clinical trial was also shown that NAC can prevent anti-TB drug-induced hepatotoxicity [21-28]. Complications of anti-TB drugs, especially liver toxicity are an important issue in Iran. The results of this study show that the administration of NAC during first month treatment of Tuberculosis lowers the hepatotoxic effect of anti-TB drugs. Patients in trial group had better quality of life and had more reduction of CRP level and Therefore it is recommended that NAC need to be as potential adjuvant therapy along with anti-TB drugs to prevent and reduced incidence, duration and severity of hepatotoxicity and also improve patient compliance, quality of life and disease outcome. Also due to the limited sample size, it is recommended that similar studies be conducted with larger samples.

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