Effectiveness of Garlic Tablet Compared with Rifampin in the Treatment of Brucellosis

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Abstract: *Background:* Studies carried out about anti-brucella properties of *Allium sativum* both *in vitro* and *in vivo* is provided. In this clinical trial, we test garlic extracts tablet effectiveness in the treatment of acute brucellosis though prevent of increase drug resistance against rifampin as main drug of anti-tuberculosis. *Method:* In this double blind case control study 36 patients as cases group recieved doxycycline 200mg daily, garlic tablet 1200 mg daily, for 6 weeks plus gentamicin 5mg/kg/day for one week and 36 patients as control group recieved rifampin 600 mg daily, doxycycline 200 mg daily for 6 weeks plus gentamicin 5 mg/kg/day for one week. Patients were followed for up to 9 months for treatment failure or relapse. Data collected and analyzed with spss (ver. 18). *Result:* Sixty nine patients complete study, 34 patients in trial group and 35 patients in control group. Mean age of cases was 40.2 ± 17.1 and in control group 40.1 ± 15.9. Treatment failure in trial group was 8.8% and in control group was 7.8%. There was no significant difference in response rate between two groups (P=0.6191). Relapse after 9 months was 14.7% in trial group and 8.6% in control group (p=0.4290). *In Conclusion:* There were no meaningful differences in response and failure rate of garlic and rifampin groups. So regarding same response and less complication of garlic, substitution of garlic for rifampin in the treatment of brucellosis is recommended. Multi center and larger group of patients is needed for definite conclusion.

Key words: Brucellosis · Garlic Tablet · Rifampin

INTRODUCTION

Brucellosis is a major health problem in Mediterranean and Middle East countries. WHO has estimated that worldwide new cases of brucellosis is more than 500000 per year [1]. Although Brucellosis is controlled in many developed countries, it has remained a major health problem in developing nations. The causing agent, a cocobacillus is an aerobe, non-motile, non-spore forming bacteria [2]. There are different types including *Brucella melitensis*, Abortus, Suis, Canis, Ovis, neotoma and Maris which the first four of them are pathogenic in humans. Most invasive and pathogenic of them is *Brucella melitensis* that is responsible for most cases of brucellosis

worldwide and in Iran. *B. abortus* is milder and *B. canis* is least pathogenic for humans. *B. suis* is usually the cause of deep abscesses [3, 4].

Brucellosis is seen across the world but most commonly in Mediterranean (South Europe, north and east of Africa), Middle East, India and Central Asia. For years the disease existed in Iran and in Markazi province with incidence rate of 98-130 per 100000 which indicates high incidence and prevalence rate [5]. Brucellosis in humans have acute, subacute, chronic and localized forms. The incubation period is from 1-6 weeks to several months [6].

Symptoms of acute illness included; fever, chills, headache, myalgia, joint pain, weakness, fatigue, nausea, perspiration at night and anorexia. Brucellosis is a

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multisystem disease and involvement is reported in the gastrointestinal, cardiovascular, hematopoietic, neurologic, pulmonary, integumentary and ophthalmic systems [7]. Hematologic disorders are seen as anemia, leukopenia, thrombocytopenia, bicytopenia, pancytopenia, acute hemolysis and sometimes Disseminated Intravascular Coagulation [8].

There were several treatment regimens for brucellosis. In a meta-analysis done in 2008 Doxycycline (6wks), Rifampin (6wks) and Gentamicin (1wk), was found more effective than other regimens [9]. This is more used in Iran and in Markazi province, although clinical trials and a meta-analysis show a little superiority of Doxycycline plus Streptomycin as compared to Doxycycline plus Rifampin and this is stressed upon by the pharmacokinetic fact that blood levels of Doxycycline are higher when used with Streptomycin [10, 11], other studies show that Doxycycline plus Rifampin is preferred both by physicians and patients [12,13]. Furthermore long term treatment both with Rifampin and Streptomycin has been shown to increase resistance to mycobacteria in endemic areas and significance of this resistance may be more important than the collective complications of brucellosis [14, 15].

Garlic "*Allium Sativum*" was prescribed since ancient times in the Persian, Egyptian, Greek and Chinese medicine. It has several antibacterial effects and regulates the immune system and improves cellular immunity against intracellular pathogens. Probably with its direct effect on smooth muscle of vascular wall, garlic causes vasodilation of peripheral vessels. It can also activate nitric oxide synthase and hence lower the blood pressure. It also has an effect in lowering cholesterol and triglyceride by inhibiting the key enzymes in its synthesis. Garlic also regulates the cell wall and plasma phospholipids and decreases LDL and VLDL and increases HDL. Garlic prevents clotting by increasing the fibrinolytic activity, increasing the clotting time and delaying the platelet aggregation [16]. It has been long used in infections. Today it is supplied as Tablets, capsules and drops. Its antibacterial effect is related to sulfinated compounds like Aliin, Alicine and Alistaene and for the same reason it is effective against gram positive and negative bacteria, parasites, fungi and viruses. Besides being an antimicrobial agent, garlic has anti-inflammatory and anti-oxidant effects [17].

Considering the importance of Rifampin in the treatment of TB and hig1h prevalence of brucellosis in Iran and its Markazi province and also high endemicity of TB in this region, it is necessary to replace Rifampin in

brucellosis with an agent with less side effects, better tolerance and less risk of resistance. The aim of this clinical trial is to compare one of the most effective treatment regimens (Doxycycline 6wks, Rifampin 6wks, Gentamicin 1 wk), with Doxycycline 6 wks, Garlic extract tablet 6wks plus Gentamicin 1wk for substitution of garlic for rifampin in the treatment of brucellosis.

MATERIALS AND METHODS

This is a double blind clinical trial. Sample size was calculated 72 patients, considering with a power of 80% and alpha 0.05 and the results of some studies reporting the rate of relapse in case of doxycycline plus Rifampin being 10% [15]. After written informed consent obtained from all patients to enter the study 36 patients in the case group received Doxycyline 200 mg daily for 6 wks and Gentamicin 5mg/kg for one wk plus 6 wks of garlic tablet extract 1200mg daily (each tablet 400mg contain 1200 microgram of Aliin and Alicin equal to 2000 mg of fresh garlic) and 36 patients in the control group received 200 mg Doxycycline daily and 600mg Rifampin Daily for 6 wks plus 5mg/kg of Gentamicin for one wk. Patients assigned randomly in the trial and control group. During the study two patients left the trial group due to allergy to garlic and one patient left the control group due to intolerance to Doxycycline and eventually 69 patients completed the study. Then patients were compared of disappearance of symptoms (fever, arthralgia, malaise) and decrease in CRP and Wright and 2ME titers and followed for 9 months for relapse. The inclusion criteria were the clinical symptoms of brucellosis plus positive culture or PCR and or serology of standard tube agglutination=1:160 plus wright 2- mercaptoethanol=1:40. The Exclusion criteria were: age of less than 15 yrs; history of brucellosis treatment within the past 2 yrs; chronic brucellosis; Pregnancy; aquired or innate immunodeficiency; allergy to garlic; local brucellosis (e.g endocarditis, spondylitis…); concurrent advanced illness like chronic renal, cardiac, pulmonary or hepatic condition.

Data were collected by check lists and summarized in data sheets then with SPSS (ver.18) were analyzed. Categorical variables in two groups were compared by the chi-square or Fisher exact test and a two-sample t test or Mann-Whitney test for continuous variables. P-value less than 0.05 was considered significant. This research was authorized by research and ethics committee of Arak University of Medical Sciences and registered with www.irct.ir (IRCT201305179855N4).

RESULTS

Seventy two patients enrolled in this clinical trial, but 69 patients (34 in trial group, 35 in control group) completed the study. Twenty-three male (67.7%) in trial and 22 (62.9%) in control group enrolled (p=0.6755). 79.4% of trial and 74.3% in control group were rural. Mean age of trial group was 40.2±17.1 and median age was 39 years and in control group mean age was 40.1±15.9 with median age 42 years. Also 19 (55.9%) patients in trial group and 21 (60%) patients in control group had history of contact with cattle and had consumed unpasteurized dairy (P-Value = 0.7301).

Treatment failure in trial was 3 (8.8%) and in control group 2 (5.7%).There was no meaningful difference in response rate between 2 groups (P=0.6191). Relapse after 9 months follow up was 5(14.7%) in trial and 3 (8.6%) in control group (p=0.4290). Clinical and laboratory findings are shown in table 1 and 2.

DISCUSSION

This study clarifies that therapeutic effect of garlic compared to rifampin was significant and altogether shows no difference in improving laboratory and clinical outcomes. Also in the follow up for failure and recurrence, there was no significant difference in the trial and control groups compared to other antibiotic regimens and was acceptable. Garlic contains considerable amounts of active chemical ingredients, include amino acids such as arginine, organosulfate compounds such as aliin and alicin, minerals (Germanium, Calcium, Ferrous, Zinc, Potassium, cupper, selenium and magnesium), allinase and vitamins A, B1 and C. Physiologic action of garlic is more related to alicin (thiosulphinate diallyl). This is responsible for anti-microbial effects of garlic [18-20].

In 2002 a study of Inder and Quitang revealed that mechanism of garlic effect is mediated through blocking the activity of nuclear factor kappa. This factor increases the expression of inflammatory cytokines and is a key molecule in inflammation. Activation of this nuclear factor is mediated through signals of TLR-4 (Toll-like Receptors) [21]. Studies have shown that Garlic alicin contains thiosulfinates that reacts with the cysteine in the aforementioned receptors and inhibits signals at the cell receptor level and by inhibiting the signal of TLR-4, does not allow the activation of factor KB [22].

Many studies have been done on antimicrobial effects of garlic on *H.pylori, M.tuberculosis, S.aeroginosa,* Shigellosis, different urologic pathogens, enteric parasites, Leishmaniasis and even viruses and fungi [23-30].

In a study performed by Shapoori et al from Iran about antimicrobial effect of garlic chloroformed extract (Alicine) on *B. melitensis* (rev-1) and *B. abortus* (S-19), first the chloroformed extract was made and then after quantifying the amount of Alicin, minimum inhibitory concentration and minimum bactericidal concentration was defined in cases of two types of brucella using the dilution in tube and diffusion in agar. This study showed that the bactericidal effect of alicin is not temperature dependent and the bactericidal effect is manifest in the first two hours. Also this study shows that Alicin exerts effect even in the bacteria which is inside the macrophage and eliminate it. Considering the effect of garlic in the activation of macrophages and T cells and the role of these cells against brucella, could be considered at least an adjunct in the treatment of brucellosis [31,32].

In the study of Saba A.S.H. et al from Turkey named "comparing the activity of aqueous garlic extract in vitro with other antibiotics (tetracycline, rifampin, streptomycin) against *Brucella melitensis*", showed considerable effect of raw extract compared to antibiotics [33]. The results of these two studies show that garlic extract can inhibit brucella in vitro. The effect of Doxycycline plus Rifampin regimen was different in various studies and in a meta- analysis the failure rate was 7.8% (3.1%-15%) and the recurrence rate was 10.7% (3.3%-16%) [34]. In our study the failure rate was 8.8% in the case and 5.7% in the control group and was not statistically significant. Also there was no meaningful difference in the failure rate of the case group with the failure rate of Doxycycline plus rifampin in different studies (7.8%). (p=0.7948) Considering recurrence in some studies it was 10.7%. In our study it was 14.7% in the trial and 8.6% in the control group and there was no meaningful difference between them and in comparison with other studies recurrence rate (mean=10.7%) with Doxycycline plus rifampin regimen shows no meaningful difference (p=0.3953).

Garlic as mentioned in some literature as a natural antibiotic, has little side effects and acceptable to patients. The only consideration is allergy in some patients which was the cause of leaving the study in two of our patients. In other instances it was easily tolerated. In 6 patients minor dyspepsia and nausea was reported which was relieved by taking the tablet with food.

Table 1: Clinical and laboratory findings in trial and control group before treatment

	Group		
Sign and symptom	Trial	Control	p-value
Fever	30(88.2%)	32(91.4%)	0.6603
Sweating	24(70.6%)	23(65.7)	0.6624
Arthritis and Arthralgia	21(61.8%)	22(62.9%)	0.9249
Constitutional symp.	11(32.4%)	10(28.6%)	0.7317
Anemia	8(23.5%)	10(28.6%)	0.6312
Leucopenia or Leucocytosis	11(32.4%)	12(34.3%)	0.8650
Throbocytosis or Thrombocytopenia	7(20.6%)	6(17.1%)	0.7114
Increase ESR	14 (41.2%	16(45.7%)	0.7039
Positive CRP	24(70.6%)	27(77.1%)	0.5352

Table 2. Clinical and laboratory findings in trial and control groups at the end of the sixth week of treatment.

	Group		
sign and symptom	Trial	Control	p-value
Fever	0	0	
Sweating	2(5.9%)	2(5.7%)	0.9760
Arthritis and Arthralgia	2(5.9%)	1(2.8%)	0.5352
Constitutional symp.	2(5.9%)	2(5.7%)	0.9760
Anemia	4(11.7%)	5(14.3%)	0.7566
Leucopenia or Leucocytosis	2(5.9%)	2(5.7%)	0.9760
Thrombocytosis or Thrombocytopenia	1(2.9%)	0(2.9%)	0.3077
Increase ESR	2(5.9%)	1(2.8%)	0.5352
Positive CRP	3(8.8%)	2(5.7%)	0.6423
Wright >1/80	28(82.4%)	27(77.1%)	0.5892
2ME>1/40	27(79.4%)	26(74.3%)	0.6170

CONCLUSION

Results of this study shows that garlic tablet could have a role in the treatment of brucellosis. Six weeks of Doxycycline plus garlic tablet with 1 weeks of Gentamicin is as effective as six weeks of Doxycycline plus Rifampin with one week of Gentamicin. Both TB and brucellosis are endemic in Iran and Rifampin is used in TB and it is advised to avoid using rifampin in the treatment of brucellosis in endemic areas of TB. Considering lower side effects, garlic can replace rifampin in the treatment of brucellosis.

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