who are released from the ED without further evaluation. This accounts for nearly 20% of reported malpractice in EDs of United States.1 Atherosclerosis (as a main cause of acute coronary syndrome) and its thrombotic complications are the leading causes of mortality and morbidity in developed countries, where cardiovascular disease is responsible for 41.4% of deaths and is the leading cause of mortality.2-4 In Iran, cardiovascular disease is the leading cause of mortality and is responsible for 46% of deaths.4-6 Acute coronary syndrome (ACS) is referred to a spectrum of coronary artery diseases, including unstable angina (U/A), ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). The term “acute coronary syndrome” is a useful one, because the initial presentation and early management of U/A, STEMI and NSTEMI frequently are similar. Differentiating ACS from non-cardiac chest pain is the primary diagnostic challenge.7 Inflammation seems to be a major final step in ACS.8 The advent of a highly sensitive assay for CRP

INTRODUCTION

Angina pectoris (chest pain) is a common problem and a difficult challenge for clinicians. More than 5 million patients are examined yearly in emergency departments (ED) of United States, with 6 billion dollars cost. Although only 25-50% of patients with chest pain are not appropriately admitted to the hospital, acute myocardial infarction and coronary heart disease are misdiagnosed up to 8% of patients with acute chest pain

ABSTRACT

Background: Cardiovascular disease is the leading cause of mortality. The previous findings which suggest the reduction in C-reactive protein (CRP) levels by statin encouraged us to conduct the present study in which we tested the effects of atorvastatin, on levels of hs-CRP in a prospective randomised clinical trial study on patients with acute coronary syndrome. Materials and Methods: Present prospective randomised clinical trial study conducted on 180 patients who had developed coronary artery disease and presented in emergency departments of Educational-Medical centers of Tabriz University of Medical Sciences. The patients were divided randomly into two groups and then two therapeutic protocols were given to them. One group medicated by high-dose atorvastatin (40 mg) and the other group received low-dose atorvastatin (20 mg). All variables were collected by questionnaires and were analyzed. Results: There were 180 patients consisted of 34 females and 56 males in low-dose atorvastatin group (L-DA group), and 30 females and 60 males in high-dose atorvastatin group (H-DA group) (P = 0.533). In this study atorvastatin in high doses decreased hs-CRP levels about 40% and in low doses it only caused decrease of 13.3%, and significant correlation was observed between two groups (Paired Sample T-test) (P = 0.001). Also atorvastatin in high doses decreased LDL levels about 23% and in low doses it only decreased 10%, and significant correlation was observed between two groups (Paired Sample T-test (P = 0.001). Atorvastatin in high doses decreased HDL levels about 9% and in low doses it only decreased 6%, and again significant correlation was observed between two groups (P = 0.009). Conclusion: The present study confirms the novel observation that atorvastatin therapy results in a significant reduction in hs-CRP levels. Key words: Atorvastatin, acute coronary syndrome, chest pain, hs-CRP
has resulted in a greater understanding of the role of inflammation in coronary artery disease.\textsuperscript{9,10} Elevated serum CRP on admission is a marker for anatomic complexity of ischemic lesions and indication for revascularization in U/A.\textsuperscript{11} Several studies have demonstrated that high-sensitivity CRP (hs-CRP), measured at either admission or discharge, may have prognostic value in patients with ACS. The development of hs-CRP assays has caused to exploration of the role of this acute phase reactant in predicting cardiovascular events.\textsuperscript{12} Prospective studies indicate that baseline levels of CRP, the prototypic marker of inflammation, are associated with an increased risk of cardiovascular events. To our knowledge, limited studies have evaluated the medications influencing high-sensitive CRP (hs-CRP) levels, especially in high-risk patients. Prospective studies have confirmed the presence of a positive consistent association between hs-CRP and future coronary events.\textsuperscript{12} Clinical trials with hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins) demonstrated a significant reduction in cardiovascular events. Atorvastatin (statins) therapy resulted in a significant reduction in hs-CRP levels.\textsuperscript{9} The previous findings in clinical science in cardiovascular medicine which suggest the reduction in CRP levels by statins\textsuperscript{9,13} encouraged us to conduct the present study in which the effects of atorvastatin, on levels of hs-CRP in a prospective randomised clinical trial study on patients with ACS was tested.

**MATERIALS AND METHODS**

Present prospective randomised clinical trial study conducted on 180 patients who had developed coronary artery disease and presented in ED of Educational-Medical centers of Tabriz University of Medical Sciences. All patients with chest pain in whom the acute coronary syndrome was diagnosed by electrocardiogram (ECG) and serum cardiac marker determinants were enrolled into study. Exclusion criteria were as following: Not drug consumption within study and not agreement with the study.

The patients were divided into two groups randomly and then two therapeutic protocols were given to them. These protocols were approved by the Institutional Review Board, and all patients signed informed consent. One group medicated by high-dose atorvastatin (H-DA group; 40 mg) and the other group received low-dose atorvastatin (L-DA group; 20 mg). All variables were collected by questionnaires and were analyzed. These variables were included demographic data (age, sex, residence location, etc), cardiac risk factors [smoking, exercise, alcohol or opioid abuse, obesity (BMI>30), diabetes, hypertension and family history] and primary and secondary hs-CRP and lipid profile, anemic disorders and coagulation disorders. We measured baseline plasma concentrations of hs-CRP, lipid profiles [total cholesterol (T-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides], serum cardiac marker determinants and ECG at entry and after 3 months of therapy. During this period we followed up the patients by echocardiography and measured ejection fraction (EF) within 8 weeks.

**RESULTS**

During present trial, 180 patients who developed ACS consisted of 34 females and 56 males in L-DA group, and 30 females and 60 males in H-DA group were observed. No significant correlation was observed between two groups (\(P = 0.53\)). The salient characteristics of the participants in this study are as following: Their mean age in L-DA group was 60.60 ± 7.87 years and in H-DA group was 57.58 ± 8.13 years. Final diagnoses in H-DA group were U/A in 65 cases (72.2\%), NSTEMI in four cases (4.4\%), and STEMI in 21 cases (23.3\%); and in L-DA group they were U/A in 67 cases (74.4\%), NSTEMI in four cases (4.4\%) and STEMI in 19 cases (21.1\%). In 12 cases of H-DA group and two cases of L-DA group, familial history was positive. We observed a significant correlation between two groups (\(P = 0.005\)). In L-DA group, 37 cases had history of hypertension, 11 cases had history of diabetes, 7 cases had hyperlipidaemia and 22 cases had cigarette smoking history. In H-DA group 37 cases had history of hypertension, 10 cases had history of diabetes, 13 cases have hyperlipidaemia and 13 cases had cigarette smoking history. No significant correlation was observed between two groups. History of heart disorders was positive in two cases of L-DA group and four cases of H-DA group, and no significant correlation was found between them (\(P = 0.73\)). There was no history of anaemia and coagulation disorders among the two groups. Also, in L-DA group, 26 cases had history of PCI, 11 cases had history of CABG and 20 cases had history of CAG. In H-DA group, 26 cases had history of PCI, five cases had history of CABG and 25 cases had history of CAG. No significant correlation was observed between two groups (\(P = 0.24\)). After an 8-week period of follow up, in L-DA group, 81 cases were improved and eight cases (8.9\%) involved acute coronary syndrome and one case died; but in H-DA group, 85 cases were improved and five cases involved acute coronary syndrome. No significant correlation was observed between two groups (\(P = 0.43\)). We calculated EF during follow-up period and obtained the following results: EF in 72 cases (80\%) of L-DA group was normal and in 18 cases (20\%) decreased; and in H-DA groups, EF was normal in 66 cases (73.3\%) and decreased in 24 cases (26.7\%). No significant correlation was found between two groups (\(P = 0.09\)). In this study atorvastatin in high doses decreased hs-CRP levels about 40\% and in low doses it only decreased 13.3\%, and significant correlation was observed between two groups (Paired Sample T-test) (\(P = 0.001\)) [Table 1]. Also atorvastatin in high doses decreased LDL levels about 23\% and in low doses only decreased 10\%, and significant correlation
was observed between two groups (Paired Sample T-test) \((P = 0.001)\) \([\text{Table 2}]\). Atorvastatin in high doses decreased HDL levels about 9% and in low doses only decreased 6%, and significant correlation was observed between two groups (Paired Sample T-test) \((P = 0.009)\) \([\text{Table 3}]\).

**DISCUSSION**

Coronary heart disease (CHD) is the most leading cause of mortality in the developed countries.\(^\text{14}\) Atherosclerosis, as the background cause of CHDs, is a process that begins early in life and worsens progressively for decades.\(^\text{12}\) Previous studies suggest that atherosclerosis is a chronic process that, from its beginning to end, involves inflammatory cells (T-cells, monocytes, macrophages), inflammatory proteins (cytokines, chemokines), and inflammatory responses from vascular cells (expression of adhesion molecules on endothelial cells). Recently, a variety of proteins have been identified whose levels predict cardiovascular risk. Of these proteins, CRP, tumor necrosis factor-alpha, and interleukin-6 have been most widely studied. The mechanism for this prediction effect on CRP remains to be unknown, and possibly it is related to secondary effects of lowering LDL-C.\(^\text{12}\) The hs-CRP has prognostic application in patients with ACS and is a strong independent predictor of coronary events in apparently healthy cases.\(^\text{12}\)

The recent trials with "hydroxymethylglutaryl coenzyme-A reductase inhibitors" (statins) suggested a significant reduction in ACS events.\(^\text{16}\) Although the majority of the effect could be given to beneficial effects on lipid profile, the statins might have additional beneficial effects. Epidemiological studies have demonstrated an increased risk of ACS with increasing CRP levels.\(^\text{7}\) In addition, studies have suggested that CRP shows the risk above that of an abnormal lipid profile.\(^\text{7,17}\) So, methods reducing inflammation and pro-inflammatory cytokines and CRP levels could be a potential additional modality in the prevention of ACS. One study tested the effects of statins (atorvastatin (10 mg/dL), on hs-CRP levels in a clinical randomised trial of 22 patients with combined hyperlipidaemia (LDL cholesterol > 130 mg/dL and triglycerides of 200-600 mg/dL) and suggested that atorvastatin decreased hs-CRP level significantly. These data support an anti-inflammatory effect of this agent and there was no relationship between reductions in hs-CRP level and LDL cholesterol.\(^\text{9}\) In accordance with over-mentioned studies, in our survey atorvastatin in high doses (40 mg) decreased hs-CRP levels up to 40% and in low doses (20 mg) just decreased as 13.3% and there was significant correlation between the two groups.

With greater clinical importance, it has been demonstrated that hs-CRP levels predict first MI and stroke. Multiple Risk Factors Intervention Trial (MRFIT) has demonstrated a direct positive relationship between hs-CRP and CHD mortality in men followed for a 17-year period.\(^\text{18,19}\) This association, however, was obvious only among smokers.\(^\text{12}\) In our study in L-DA group, 22 cases had cigarette smoking history and 13 cases had cigarette smoking history in H-DA group \(\!(P > 0.05)\). A similar association between hs-CRP and future ACS was found in the Cardiovascular Health Study and Rural Health Promotion Project, which included men and women over 65 years of age with subclinical cardiovascular disease.\(^\text{20}\) The Physicians' Health Study (PHS) demonstrated similar positive association between hs-CRP and future coronary events in apparently healthy men.\(^\text{21,22}\) In our study, after 8 weeks of following up, in L-DA group, 81 cases were improved and eight cases (8.9%) were affected by ACS and one case died but in H-DA group, 85 cases were improved and five cases were affected by ACS. No significant correlation was found between two groups. A randomised double-blind intervention study which was performed among 90 patients with ACS, revealed early and highly significant reductions in plasma concentrations of CRP levels by using 40 mg/dL of atorvastatin given for a month and also an early significant reduction in T-C and LDL-C. There was a 2-fold increase of events in the placebo group after 30 days.\(^\text{23}\) In the present study atorvastatin in high doses decreased LDL levels about 23% and in low doses it only decreased 10%, and significant correlation was observed between two groups. Also, atorvastatin in high doses decreased HDL levels about 9% and in low doses it only decreased 6%, and significant correlation was

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**Table 1: The changes in mean hs-CRP before and after using Atorvastatin**

| Groups                | Items                  | hs-CRP Level | hs-CRP Decrease (%) | \(P\)  |
|-----------------------|------------------------|--------------|---------------------|-------|
| High-dose Atorvastatin (mg) | primary hs-CRP         | 4.2±7.30     | 40                  | 0.001 |
|                       | hs-CRP after 3 months  | 2.4±1.77     |                     |       |
| Low-dose Atorvastatin (mg) | primary hs-CRP       | 3.0±2.53     | 13.3                |       |
|                       | hs-CRP after 3 months  | 2.5±2.6      |                     |       |

**Table 2: The changes in mean LDL before and after using Atorvastatin**

| Groups                | Mean value | LDL level | LDL Decrease (%) | \(P\)  |
|-----------------------|------------|-----------|-----------------|-------|
| High-dose Atorvastatin (mg) | LDL - primary | 104.9±11.54 | 23              | 0.001 |
|                       | LDL - secondary | 82.1±10.84 |                 |       |
| Low-dose Atorvastatin (mg) | LDL - primary | 95.8±13.75  | 10               |       |
|                       | LDL - secondary | 79.5±13.38  |                 |       |

**Table 3: The changes in mean HDL before and after using Atorvastatin**

| Groups                | Mean value | HDL level | HDL Increase (%) | \(P\)  |
|-----------------------|------------|-----------|-----------------|-------|
| High-dose Atorvastatin (mg) | HDL - primary | 37.3±9.3  | 9                | 0.001 |
|                       | HDL - secondary | 40.8±14.65 |               |       |
| Low-dose Atorvastatin (mg) | HDL - primary | 38.7±3.84 | 6               |       |
|                       | HDL - secondary | 41.3±8.37  |               |       |
observed between two groups. It is well known that in ACS, many patients have an intense inflammatory process. A study on ACS patients demonstrated that the early use of high dose of atorvastatin (80 mg/dL) decreased inflammatory markers compared with placebo in 4 months. Also, a prospective, randomised study showed a rapid effect at discharge and at 30 days after use of high dose of atorvastatin (40 mg/dL). Another observation was the spontaneous CRP level reduction in placebo groups.

Although after the first 24 hours following infarction, T-C and LDL-C are reduced because of an acute phase reaction but lipid levels do not begin to return to baseline levels until several days later. This showed that 40 mg/dL atorvastatin reduced significantly LDL-C levels at 3 months. However, this study suggested a significant association between the decrease in CRP levels and LDL-C. MI, nonfatal MI, resuscitated cardiac arrest, worsening angina, or death at 16 weeks. In the present study, after 8 weeks of following up, in L-DA group, 81 cases were improved, eight cases (8.9%) involved acute coronary syndrome and one case died; but in H-DA group, 85 cases were improved and five cases involved acute coronary syndrome. No significant correlation was observed between the two groups. In the present report, we confirm that atorvastatin therapy results in a significant reduction in hs-CRP levels. There was a significant difference between the L-DA and H-DA regarding reductions in hs-CRP. Despite the Cholesterol and Recurrent Events (CARE) study, we showed significant correlations between LDL cholesterol, or HDL cholesterol and hs-CRP levels. This study explored a potential mechanism by which statins may result in a significant reduction in hs-CRP levels.

CONCLUSIONS

In conclusion, the present study confirms the novel observation that atorvastatin therapy results in a significant reduction in hs-CRP levels. Further studies need to be directed towards elucidating the mechanism of reduction in CRP. It should be recommended for any institution to identify specific and shared protocols and strategies for management of patients with chest pain. These should include basal clinical evaluation, serial ECG and the use of specific and sensitive myocardial markers such as hs-CRP.

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How to cite this article: Zamani B, Saatlo BB, Naghavi-Bezhad M, Taqizadeh-Jahed M, Alikhah H, Abbasnezhad M. Effects of high versus low-dose atorvastatin on high sensitive C-reactive protein in acute coronary syndrome. Niger Med J 2014;55:490-4.

Source of Support: Nil, Conflict of Interest: None declared.