The Effect of Atrovastatin on Inflammatory Markers in Sulfur Mustard Gas Induced Bronchitis; A Randomized Double-Blinded, Placebo-Controlled Clinical Trial

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Abstract

Background: This study was conducted to evaluate the anti-inflammatory effect of atorvastatin in patients with chronic bronchitis due to sulfur mustard gas inhalation.

Methods: In this randomized double-blinded clinical trial we enrolled patients with chronic bronchitis due to sulfur mustard gas inhalation. Ninety man aged between 45 to 75 years with diagnosed of chronic bronchitis due to exposure to mustard gas during the Iran-Iraq war, were randomly assigned to receive either atorvastatin (40 mg) or placebo, given orally once a day for 3 months. The interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), procalcitonin, highly sensitive CRP, and COPD assessment test (CAT) score in both groups compared with each other and baseline data.

Results: After 12 weeks of using atorvastatin (n=40), the level IL-6 decreased significantly (p=0.03) without any significant differences in the level of TNF-α, high sensitive CRP, and procalcitonin (P=0.31, p=0.78, and p=0.08). In placebo group (n=38), both procalcitonin and IL-6 significantly decreased after 12 weeks (P=0.002 and p<0.001), but levels of high sensitive CRP did not differ significantly and the level of TNF-α increased (p=0.006). The mean differences in levels of TNF- α, IL-6, high sensitive CRP, and procalcitonin did not differ statistically significant between the study groups after 12 weeks. Although after 12 weeks of study in both groups the CAT score have had appreciably high magnitude decrease (P<0.001), but its mean differences change wasn't significant between group (P=0.71).

Conclusions: Administration of 40 mg atorvastatin for 3 months although could not significantly change systemic inflammatory markers or quality of life in mustard gas induced chronic bronchitis.

Trial registration: IRCT, IRCT138904144312N1. Registered 16 August 2014, https://en.irct.ir/trial/4577

Background

Sulfur mustard (2-bis-chloroethyl-sulfide) is a very toxic vesicant that had been discovered in 1821 and used in the First World War (1). It can be frequently absorbed through skin, respiratory system, ocular system, and genital tract, due to its chemical alkylating compound (2). Indeed, its toxicity is attributed to the lipophilic nature that allows to quickly penetrate target tissues and alkylate proteins, lipids and nucleic acids resulting in DNA damage and cytotoxicity (3).

Unfortunately, this gas has been applied during the Iran–Iraq war between 1980 and 1988. Its result was that over 100,000 soldiers without safety protection suffered severe injuries, and roughly about 45000 of them continue to suffer long-lasting consequences of exposure (1). Since the Iran–Iraq war, a lot of Iranian veterans have been admitted with clinical manifestations of chemical gas poisoning, especially sulfur mustard (4). These patients mostly suffered respiratory problems including chronic bronchitis and asthma, as the greatest causes of long-term disability (5-7).

Both experimental and human trials demonstrate an involvement of inflammatory cells and mediators in sulfur mustard induced lung injury. For example, animal studies on rodents and pigs showed that exposure to sulfur mustard gas increase inflammatory cells in the upper and lower respiratory track for weeks to months (8-13). Likewise, increased numbers of neutrophils and eosinophils are observed in the lung of the human for a long time after exposure (14, 15). It has not been elucidated yet whether the specific role of these inflammatory cells in sulfur mustard induced toxicity. In other models of lung injury, macrophages released inflammatory mediators which have been played a key role in the pathogenesis of toxicity (16), so it seems that they may play a similar role in the pulmonary response to sulfur mustard.

Hydroxymethyl-glutaryl (HMG) coenzyme A (CoA) reductase inhibitors (statins) have several modulatory effects especially on neutrophils, including modulation of the innate and adaptive immune systems and reduction of neutrophil migration (17-19). This is supported by previous findings that statins suppress major histocompatibility complex class II (MHC-II)–mediated T cell activation, to modulate host inflammatory cell recruitment, and then downregulating activation of the early inflammatory response gene nuclear factor B (20).

We postulated that statins would improve symptoms in patients with chronic bronchitis by reducing airway inflammation. The aim of our study was to evaluate the anti-inflammatory effect of atorvastatin in patients with chronic bronchitis due to sulfur mustard gas inhalation. We chose atorvastatin because it has a low side effect profile, and it seems that anti-inflammatory effects of atorvastatin are more than simvastatin (21).

Methods

Trial design

The present study was designed as is a two group parallel randomized double-blinded, placebo-controlled trial, and we recruited patients with chronic bronchitis due to sulfur mustard gas inhalation who were referred to the pulmonary clinics affiliated with Foundation of Martyrs and Veterans Affairs, Shiraz, Iran. The study protocol was approved by the institutional review board (IRB) of Shiraz University of Medical Sciences and we obtained ethics approval from the local ethics committee before the study was commenced. All the participants gave their informed written consent. The trial was registered with the Iranian Clinical Trials Registry (IRCT138904144312N1; www.irct.ir).

Participants

Consecutive men aged between 45 to 75 years with diagnosed of chronic bronchitis due to exposure to mustard gas during the Iran-Iraq war in outpatient clinic, were enrolled in the study (chronic bronchitis characterized by a cough productive of sputum daily for over three months' duration during two consecutive years and airflow obstruction). Exclusion criteria included had a history of exacerbation of symptoms in the past 4 weeks, connective tissue disease, sarcoidosis, eosinophilic granuloma, pneumoconiosis, lymphoma, carcinomatous, active tuberculosis, chronic liver disease, and currently on statins or who had used them within last 3 months. In addition, current smokers or former smokers who had stopped smoking less than 1 year previously were excluded from the study.

Interventions & outcomes

The patients were randomly assigned to receive either atorvastatin (40 mg) or placebo (starch pills, which were made by Shiraz Pharmacology School), given orally once a day for 3 months. The shape and packing of both pills was similar, so patients and the study investigators were blinded as to the treatment group assignment.

Initial data regarding age, body mass index (BMI), heart rate, respiratory rate, systolic and diastolic blood pressure, and drug history of the patients were recorded by a date gathering form. In addition, blood tests including total cholesterol, triglyceride (TG), liver-function tests (LFTs), and hemoglobin (Hb) were recorded at baseline. The primary outcomes were systemic inflammation status at 3 months compared with baseline, measured by white blood cell (WBC) count, amounts of interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α). Also, we considered COPD assessment test (CAT) as secondary outcomes. CAT is a patient-completed instrument to assess and quantify health-related quality of life and symptom burden in patients with COPD. It consists of 8 questions, each presented as a semantic 6-point (0–5) differential scale, providing a total score out of 40; Higher scores indicate a more severe impact of COPD on a patient’s life. (22).

Measurements

All assessments were performed at baseline and the end of intervention. The IL-6 and TNF-α, concentrations were measured with enzyme linked immunosorbent assay (ELISA) commercial kits (Platinum, Austria) according to the instructions of manufacturer. The high sensitive CRP concentration was measured with enzyme linked immunosorbent assay (ELISA) commercial kits (Diagnostics Biochem Canada Inc., Canada) according to the instructions of manufacturer. The procalcitonin (PCT) level was measured via an automatic analyzer, the VIDAS® B.R.A.H.M.S PCT assay (bioMérieux, Marcy L'Etoile, France). BMI was calculated using the weight and height measurements. Blood pressure was measured after a 5-min resting period with the individual sitting in a chair and determined using a standard mercury sphygmomanometer. Moreover, the total CAT score was calculated for each patient by summing the points for each variable.

Randomization

Randomization sequence was created using random block sizes of 4 and 6. On the order of referral, the participants were allocated 1:1 into two groups. Study pills were allocated in separate packs blinded and labeled using a four-digit code. The information regarding which codes correspond to what treatment was maintained by the project coordinator. Apart from the project coordinator, patients, attending physicians, staff involved in the pulmonary clinics, and members collecting and analyzing data were blinded to the intervention allocation.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). We estimated that a total of 90 participants would be needed to detect a difference between groups, with a two-tailed α of 0.05 and a (1-β) of 0.80, for a comparison of 2 independent mean of outcome with effect size of 0.6. The *Kolmogorov-Smirnov test* was used to test normality of variables' distribution. The baseline characteristics of both groups were compared using X2 tests or Fisher's exact test for proportions. For continuous variables, independent groups were compared using the t-test or Mann-Whitney test, whereas paired compared comparison was made using paired t-test or Wilcoxon test. Data are reported as means ± SD. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Out of the 90 patients assessed for eligibility, one individual declined further participation. Thus, the final number of patients being randomized into two study groups was 89 (45 patients in atorvastatin, and 44 patients in placebo groups). Three participants in the placebo group and two participants in atorvastatin group left the study due to personal reasons and three patients in each group were lost to follow-up. Finally, 40 patients were enrolled in atorvastatin group and 38 individuals were enrolled in placebo group (Figure 1).

The mean age of the patients were found to be 50.3±5.7 (range 45–71) years and the mean BMI of the patients were 26.1±5.1 kg/m^2. The baseline characteristics of the patients are reported in four main categories including demographics & clinical, blood tests, systemic inflammation markers, quality of life and medications (Table 1). Except for lower serum ALT (U/ml) in atorvastatin group, there was no significant difference between two study groups regarding baseline characteristics. The mean CAT scores were 29.4±7 with range 13 to 40 in atorvastatin group and 28.1±6 with rage of 14 to 40 in placebo group (P=0.36).

There was no statistically significant difference between treatment interval regarding white blood cells (WBCs) in the atorvastatin group (P=0.96), and also in the placebo group (P=0.93). In other word, compared with the placebo group, WBC wasn't significantly changed in the atorvastatin group at the end of study (P=0.93). Thereafter, the effects of atorvastatin and placebo on the serum levels of TNF-α, IL-6, high sensitive CRP, and procalcitonin were investigated after 12 weeks of treatments. After 12 weeks of using atorvastatin, the level IL-6 decreased significantly (p=0.03) without any significant differences in the level of TNF-α, high sensitive CRP, and procalcitonin (P=0.31, p=0.78, and p=0.08). In placebo group, both procalcitonin and IL-6 significantly decreased after 12 weeks (P=0.002 and p<0.001), but levels of high sensitive CRP did not differ significantly and the level of TNF-α increased (p=0.006). The mean differences in levels of TNF- α, IL-6, high sensitive CRP, and procalcitonin did not differ statistically significant between the study groups after 12 weeks. Table 2 shows changes in inflammatory markers after 12 weeks within atorvastatin and placebo groups and between the groups.

We compared the changes of CAT score after the study interventions in each groups. Although after 12 weeks of study in both groups the CAT score have meet minimum clinically important difference of a 2-unit reduction (P<0.001), but its mean differences change wasn't significant between group (P=0.71) (Table 2).

Discussion

This study is the first study that evaluates the effect of atorvastatin on systemic inflammatory markers and quality of life in mustard induced bronchitis which designed randomized, controlled, and double-blinded.

The primary goal of our study was to evaluate the hypothesis that Atorvastatin could reduce inflammatory markers in patents with mustard gas induced chronic bronchitis, but this study could not find significant reduction in Atorvastatin group inflammatory markers (IL6, TNF-α, HsCRP, and procalcitonin) at the level of 5%. Nevertheless the serum levels of IL6 and TNF-α increased significantly in control group.

Many studies had previously shown the anti-inflammatory effect of statin(23, 24), but few studies could not demonstrate this effect (25, 26). Considering the significant reduction in serum cholesterol level in Atorvastatin group it is unlikely that poor adherence to the study protocol could explain the failure to reach statistical difference between groups. The lipid lowering effect of statins is independent of CRP lowering effect (23). The benefit of intensive statin therapy is likely due to reducing level of both LDL and CRP. In contrary to Devaraj et al(23) that had postulated the early benefit of statins may be related to reduction of CRP presented preceding to their lipid lowering effect, our results shown lipid lowering effect without statistically significant reduction in HsCRP. The optimal level of statin relative to the goals of anti-inflammatory remains to be established; the anti-inflammatory effect of Atrovastatin may need higher dose or duration of usage. As already has been mentioned in method we had included patients with stable mustard gas induced bronchitis that could explain why the level of inflammatory markers were not statistically significant different between groups. On the other hand the main site of inflammation in bronchitis is lung so to be more precise, as Kaczmarek et al(25) had suggested, it might be better to assess the inflammatory marker in bronchoalveolar washing.

Although we thought the power of our study was adequate and acceptable for detecting relatively modest difference between atorvastatin and control groups, but because of wider standard deviation than expected, it is likely that this study was slightly underpowered on post hoc power analysis by G power(27).

The CAT score is a disease-specific instrument for assessing the severity of COPD (22, 28, 29). Although the CAT score of our participants meet minimum clinically important difference (30) of a 2-unit reduction in both groups (P<0.001), but its mean differences change wasn't significant between group (P=0.71). Maneechotesuwan et al have studied the

effect of simvastatin, 20 mg po daily versus placebo on sputum inflammatory markers, airway inflammation, and CAT score of 30 patients with stable COPD (31). In contrary to our findings, Maneechotesuwan et al found clinically significant important reduction in CAT score after statin. Mandal and colleagues, in a clinical trial evaluating the role of atorvastatin in treatment of bronchiectasis, reported that the patients with bronchiectasis who received statins had a better quality of life (the St George's Respiratory Questionnaire) in comparison to those had received placebo, but still not meet minimum clinically important difference of a 4-unit reduction in SGRQ score (32).

Limitations

This study had at least two major limiting factors diminishing the impact of results; first, the participants were in relatively stable state of their disease which may decrease the chance of effective anti-inflammatory of statin, second we focused on few systemic inflammatory markers in limited period of time while the main source of inflammation in patients with bronchitis is lung.

Therefore, larger prospective randomized controlled trials with long time follow up with focusing on the respiratory tract indices, like exhaled air condensate or bronchoalveolar lavage, both during stable periods and exacerbations(25) and/or other systemic inflammatory such as monocyte-macrophage function(23) is needed on the patients with chronic bronchitis due to sulfur mustard gas inhalation.

Conclusion

Despite its limitations, this study provides evidence that administration 40 mg atorvastatin for 3 months could not show significant reduction in systemic inflammatory factors in the patients with chronic bronchitis due to sulfur mustard gas inhalation.

Abbreviations

BMI; Body mass index

CAT; COPD assessment test score

CRP; C reactive protein

COPD; Chronic Obstructive Pulmonary Disease

Hb; Hemoglobin

IL-6; Interleukin 6

LFTs; Liver-function tests

PCT; procalcitonin

TG; Triglyceride

TNF-α; Tumor necrosis factor α

Declarations

Ethics approval and consent to participate:

“All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.”

Consent to publication:

Not applicable

Availability of data and materials:

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests:

The authors declare that they have no conflict of interest

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Authors' contributions:

BM, SN, and SVS were contributed in participants’ enrollment and follow them to the end of study and co-wrote the draft. SMM and BG were contributed in study design, analyzed and interpreted the patient data, and critically appraise the draft of manuscript. All authors read and approved the final manuscript.

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References

1. Nations SCotU. Report of specialists appointed by the Secretary General to investigate allegations by the Islamic Republic of Iran concerning the use of chemical weapons. Security Council of the United Nations, document S/16433, New York; 1986.
2. Willems J. Clinical management of mustard gas casualties. Ann Med Mil Belg. 1989;3(Suppl 1):1-61.
3. Ray R, Hauck S, Kramer R, Benton B. A Convenient Fluorometric Method to Study Sulfur Mustard–Induced Apoptosis in Human Epidermal Keratinocytes Monolayer Microplate Culture. Drug and chemical toxicology. 2005;28(1):105-16.
4. Taghaddosinejad F, Fayyaz AF, Behnoush B. Pulmonary complications of mustard gas exposure: a study on cadavers. Acta Medica Iranica. 2011;49(4):233.
5. SOHRABPOUR H, Masjedi M, Bahadori M. Late complications of sulfur mustard in respiratory system. Medical Journal of The Islamic Republic of Iran (MJIRI). 1988;2(3):171-4.

6. Emad A, Rezaian GR. The diversity of the effects of sulfur mustard gas inhalation on respiratory system 10 years after a single, heavy exposure: analysis of 197 cases. Chest. 1997;112(3):734-8.
7. Hoseini K, Alavi S, Abedi A. Reversibility of airflow obstruction in chronic obstructive disease secondary to sulfur mustard gas injury. 1999.
8. Kumar O, Sugendran K, Vijayaraghavan R. Protective effect of various antioxidants on the toxicity of sulphur mustard administered to mice by inhalation or percutaneous routes. Chemico-biological interactions. 2001;134(1):1-12.
9. Anderson DR, Byers SL, Vesely KR. Treatment of sulfur mustard (HD)-induced lung injury. Journal of Applied Toxicology. 2000;20(S1):S129-S32.
10. Anderson DR, Holmes WW, Lee RB, Dalal SJ, Hurst CG, Maliner BI, et al. Sulfur mustard-induced neutropenia: treatment with granulocyte colony-stimulating factor. DTIC Document; 2006.
11. Anderson DR, Taylor SL, Fetterer DP, Holmes WW. Evaluation of protease inhibitors and an antioxidant for treatment of sulfur mustard-induced toxic lung injury. Toxicology. 2009;263(1):41-6.
12. Allon N, Amir A, Manisterski E, Rabinovitz I, Dachir S, Kadar T. Inhalation exposure to sulfur mustard in the guinea pig model: clinical, biochemical and histopathological characterization of respiratory injuries. Toxicology and applied pharmacology. 2009;241(2):154-62.
13. Fairhall S, Brown R, Jugg B, Smith A, Mann T, Jenner J, et al. Preliminary Studies of Sulphur Mustard–Induced Lung Injury in the Terminally Anesthetized Pig: Exposure System and Methodology. Toxicology mechanisms and methods. 2008;18(4):355-62.
14. Beheshti J, Mark EJ, Akbaei HMH, Aslani J, Ghanei M. Mustard lung secrets: long term clinicopathological study following mustard gas exposure. Pathology-Research and Practice. 2006;202(10):739-44.
15. Rowell M, Kehe K, Balszuweit F, Thiermann H. The chronic effects of sulfur mustard exposure. Toxicology. 2009;263(1):9-11.
16. Malaviya R, Sunil VR, Cervelli J, Anderson DR, Holmes WW, Conti ML, et al. Inflammatory effects of inhaled sulfur mustard in rat lung. Toxicology and applied pharmacology. 2010;248(2):89-99.
17. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nature medicine. 2000;6(12):1399-402.
18. Mohammad S, Nguyen H, Nguyen M, Abdel-Rasoul M, Nguyen V, Nguyen CD, et al. Pleiotropic Effects of Statins: Untapped Potential for Statin Pharmacotherapy. Current vascular pharmacology. 2019;17(3):239-61.
19. Sapey E, Patel JM, Greenwood H, Walton GM, Grudzinska F, Parekh D, et al. Simvastatin Improves Neutrophil Function and Clinical Outcomes in Pneumonia. A Pilot Randomized Controlled Clinical Trial. American journal of respiratory and critical care medicine. 2019;200(10):1282-93.
20. Watts KL, Sampson EM, Schultz GS, Spiteri MA. Simvastatin inhibits growth factor expression and modulates profibrogenic markers in lung fibroblasts. American journal of respiratory cell and molecular biology. 2005;32(4):290-300.
21. Sathyapalan T, Atkin SL, Kilpatrick ES. Disparate effects of atorvastatin compared with simvastatin on C-reactive protein concentrations in patients with type 2 diabetes. Diabetes care. 2010;33(9):1948-50.
22. Jones P, Harding G, Berry P, Wiklund I, Chen W, Leidy NK. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009;34(3):648-54.
23. Devaraj S, Rogers J, Jialal I. Statins and biomarkers of inflammation. Current atherosclerosis reports. 2007;9(1):33-41.

24. Walsh A, Perrem L, Khashan AS, Henry MT, Ni Chroinin M. Statins versus placebo for people with chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2019;7(7):Cd011959.
25. Kaczmarek P, Sladek K, Skucha W, Rzeszutko M, Iwaniec T, Dziedzina S, et al. The influence of simvastatin on selected inflammatory markers in patients with chronic obstructive pulmonary disease. Polskie Archiwum Medycyny Wewnetrznej. 2010;120(1-2):11-7.
26. Emad A, Koushki A. The impact of concurrency of colchicine and simvastatin on variation of serum immunoglobulins IgG, IgE, IgM and IgA in mustard gas-wounded patients. Biosciences Biotechnology Research Asia. 2016;13(1):59-65.
27. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods. 2007;39(2):175-91.
28. Ghobadi H, Ahari SS, Kameli A, Lari SM. The Relationship between COPD Assessment Test (CAT) Scores and Severity of Airflow Obstruction in Stable COPD Patients. Tanaffos. 2012;11(2):22-6.
29. Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Kardos P, Levy ML, et al. Properties of the COPD assessment test in a cross-sectional European study. The European respiratory journal. 2011;38(1):29-35.
30. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. The Lancet Respiratory medicine. 2014;2(3):195-203.
31. Maneechotesuwan K, Wongkajornsilp A, Adcock IM, Barnes PJ. Simvastatin Suppresses Airway IL-17 and Upregulates IL-10 in Patients With Stable COPD. Chest. 2015;148(5):1164-76.
32. Mandal P, Chalmers JD, Graham C, Harley C, Sidhu MK, Doherty C, et al. Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial. The lancet respiratory medicine. 2014;2(6):455-63.

Tables

Table 1.
The baseline characteristics of the study patients

	Atorvastatin Group (n=40)	Placebo Group (n=38)	*P* value
Demographics & clinical*			
Age (years)	51±5.5	49.7±5.9	0.10‡
BMI (Kg/m^2)	27±5.5	25±4.3	0.08
Heart rate (beats/min)	78.6±9	78.9±10	0.84‡
Respiratory rate (inhalation-exhalation cycles/min)	15.7±2.3	15.1±2.3	0.23‡
Systolic blood pressure (mmHg)	115.6±14	119.2±14	0.26‡
Diastolic blood pressure (mmHg)	72.9±9	76.1±8	0.07‡
Blood tests*			
Hemoglobin (g/dl)	15.4±1.9	15.7±1.6	0.46
Serum AST (U/ml)	21.8±7	24.1±12	0.49‡
Serum ALT (U/ml)	20.6±10	28.7±19	0.007‡
Serum alkaline phosphatase (U/l)	206±47	193±49	0.23
Total Cholesterol (mg/dl)	206±42	211±85	0.74
Low-density lipoprotein (mg/dl)	124±33	119±30	0.47
TG (mg/dl)	174±89	149±114	0.25
Systemic inflammation markers*			
White blood cells (×10^3 cells per ml)	7.6±2.5	6.7±1.7	0.052
IL-6 (pg/ml) [65-52]	0.92±0.87	1.1±1.3	0.81‡
TNF-α (pg/ml) [79]	2.1±0.4	1.9±0.3	0.10‡
HsCRP (ng/ml) [62-49]	5.35±3.2	4.10±2.9	0.07
Procalcitonin (pg/ml)	0.043±0.18	0.038±0.07	0.20‡
Quality of life*			
CAT score	29.4±7	28.1±6	0.36
Medication†			

Inhaled corticosteroids	4 (10%)	5 (14.7%)	0.81
Inhaled anticholinergics	6 (15%)	4 (11.1%)	0.77
Inhaled β2 agonists	19 (47.5%)	15 (41.7%)	0.72
Antihypertensive	13 (31.7%)	13 (38.2%)	0.67
Antidiabetics	5 (12.5%)	4 (11.8%)	0.87
Mucolytic	15 (37.5%)	14 (41.2%)	0.79

* Average, Standard Deviation; †Frequency and Percentages;‡ Mann-Whitney test

Table 2.
Comparing outcomes within and between two study group

Status	**Atorvastatin Group (n=40)**			**Placebo Group (n=38)**			**Difference between groups After 12 weeks**	
	Baseline	12 weeks	P value	Baseline	12 weeks	P value	Mean Difference (95% CI)	P value
WBC ($\times 10^3$ cells/ml)	7.6±2.5	7.4±1.8	0.96	6.7±1.7	6.7±1.5	0.93	(-0.78, 0.72)	0.93
IL-6 (pg/ml)	0.92±0.87	0.69±0.7	0.03*	1.1±1.3	0.46±0.3	<0.001*	(-0.091, 0.901)	0.07‡
TNF-α (pg/ml)	2.1±0.4	2.2±0.3	0.31	1.9±0.3	2.2±0.4	0.006	(-0.330, 0.070)	0.20
HsCRP (ng/ml)	5.35±3.2	5.49±3.4	0.78	4.10±2.9	4.45±3.2	0.51	(-1.68, 1.28)	0.78
Procalcitonin (pg/ml)	0.043±0.18	0.04±0.15	0.08*	0.038±0.07	0.02±0.05	0.002*	(-0.015, 0.048)	0.15‡
CAT score	29.4±7	22±5.6	<0.001	28.1±6	19.6±7.2	<0.001	(-2.5, 3.7)	0.71
Cholestrol (mg/dl)	206±42	160±44	<0.001	211±85	180±31	<0.001	(-39.5, -8.7)	0.003
Low-density lipoprotein (mg/dl)	124±33	100±37	0.001	119±30	116±24	0.357	(-31.6, -4.7)	0.009

* Wilcoxon test; ‡ Mann-Whitney test

Figures

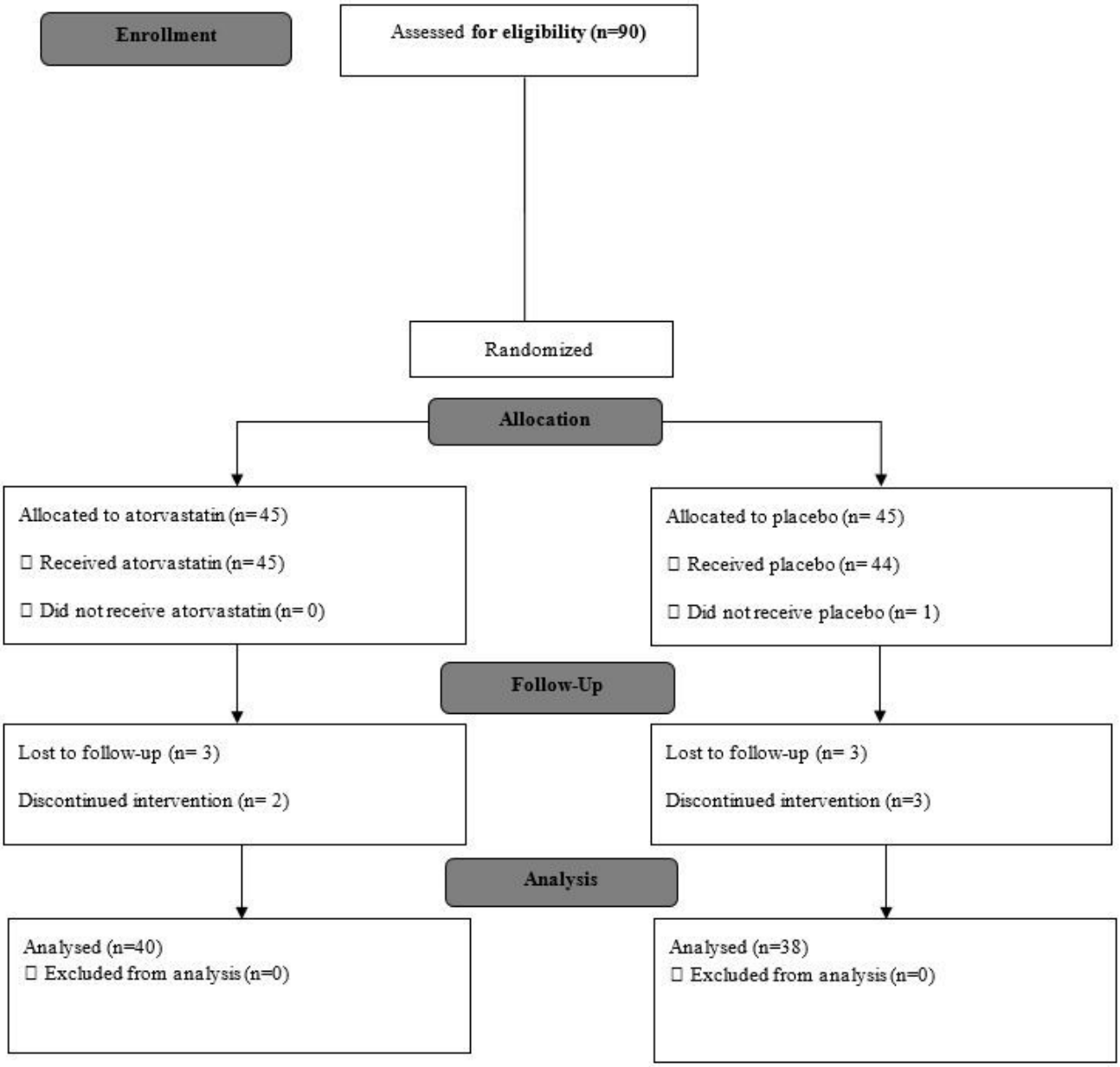

Figure 1

CONSORT 2010 study flow chart

Supplementary Files

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- CONSORT2010Checklist.doc
- rawdata.xlsx