Effect of Statin Therapy in Early Sepsis: Effect on Endothelial Function and Prognostic Implication

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Abstract

Background: Sepsis, defined as the systemic inflammatory response syndrome that occurs during infection, is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individual. HMG-CoA reductase inhibitors are potentially powerful inhibitors of the inflammatory process by a lipid independent mechanism as they are not related to lowering LDL cholesterol.

Purpose: To determine efficacy and safety of the new regimen of Atorvastatin as an adjunctive line of treatment in early sepsis as well as its effect on endothelial function and in modifying the inflammatory markers.

Methods: A total of 50 patients with early sepsis were alternatively randomized to statin group (25 patients) and received (Atorvastatin 80mg/day for 4 consecutive days, plus conventional sepsis treatment) or control group (25 patients) and received only conventional sepsis treatment and followed by: Inflammatory markers (CRP and PCT), Nitric oxide metabolites, Severity of illness as indicated by SOFA score monitoring and need for organ supportive measures, Length of ICU stay, 28 day mortality and final outcome and ALT, AST and CPK to assure the safety of statins in early sepsis.

Results:

- The mean level of CRP and PCT at day 4 significantly reduced in statin group than in control group (p value = 0.007, 0.001 respectively).
- The mean level of Nox metabolites at day 4 nonsignificantly reduced in statin group compared to control group (p value = 0.1).
- The short term high intensity Atorvastatin therapy reduce nonsignificantly the total cholesterol level at day 4 (p value = 0.1).
- The short term high intensity Atorvastatin therapy significantly reduce the development of severe sepsis as indicated by reduction of Mean SOFA score and Highest SOFA score; (p value = 0.038 and 0.043 respectively).
- The short term high intensity Atorvastatin therapy significantly reduce the need for vasopressor use in the course of sepsis (p value = 0.001) and also reduce the need for mechanical ventilation (p value = 0.044).
- The short term high intensity Atorvastatin therapy nonsignificantly reduce the length of ICU stay (p value = 0.25) and 28 day mortality (p value = 0.26).

- The short term high intensity Atorvastatin therapy are safe to be used in early sepsis regarding their effect on liver and muscle enzymes.

Conclusion: The use of a short term high intensity Atorvastatin therapy in patient with early sepsis seems to be safe and associated with promising effects on inflammatory cascade and endothelial function reflected clinically by its effect on clinical course and mortality from sepsis.

Key Words: Atorvastatin – Early sepsis – CRP – PCT – Nox metabolites.

Introduction

SEPSIS, defined by consensus conference as “the systemic inflammatory response syndrome that occurs during infection” [1-3], is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individual. Thus, basic research and clinical trials have focused on agents capable of blocking steps within the inflammatory cascade [4-9]. However, despite the multitude of therapeutic approaches evaluated, the only inflammation-modulating substances demonstrated to date to benefit patients with severe sepsis are activated protein C and low-dose hydrocortisone [10].

HMG-CoA-reductase inhibitors (statins) such as Atorvastatin have been shown to exhibit important immunomodulatory effects independent of lipid lowering [11-12]. In fact, these so-called pleiotropic effects are now considered to contribute significantly to the morbidity and mortality benefit observed in patients with coronary heart disease who are treated with statins. Pleiotropic effects have been demonstrated to comprise anti-inflammatory actions [13], improve the endothelial and microvascular functions [14] and modulate endothelial nitric oxide synthase. In particular, statins have been found to reduce the increased endothelial adhesiveness of monocytes from hypercholesterolemic individuals or after stimulation with cytokines under flow and static
Effect of Statin Therapy in Early Sepsis

This appears to be partly attributable to reduced expression of both monocytic and endothelial adhesion molecules because of selective inhibition of the integrin leukocyte function antigen-1 (LFA-1) by affecting Rho GTPases.

HMG-CoA reductase inhibitors are potentially powerful inhibitors of the inflammatory process [17]. The mechanism by which statins modulate the immune response is regarded as lipid independent as they are not related to lowering LDL cholesterol.

Statins affect the production of many acute phase reactants, such as IL-6, IL-8, TNF-α, monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP) [18]. CRP is mainly produced by hepatocytes in response to IL-6. In an in vitro study human hepatocytes were stimulated with IL-6 in the presence or absence of simvastatin and atorvastatin [19]. Hepatocytes treated with statins showed significant inhibition of IL-6-induced CRP production. The reduction of CRP levels was more pronounced with atorvastatin than with other statins [19-24].

Aim of the work:

The aim of our study was to investigate the anti-inflammatory and pleiotropic effect of short term high intensity oral statin (Atorvastatin) as an adjunctive therapy in early sepsis, to determine whether patients with early sepsis treated with statin develop severe sepsis less frequently or not, to evaluate the impact of strategy on duration of ICU stay, patient outcome and need for organ supportive measures and to evaluate the safety of Atorvastatin use in patients with early sepsis.

Patients and Methods

Patients: We prospectively enrolled fifty patients (25 males, 25 females mean age 51.6 ± 16.8) with early sepsis, admitted to Critical Care Department, Cairo University Hospitals; from Sept. 2007 to Sept. 2008.

Inclusion criteria:
1 - Age ≥ 17 years.
2- Informed consent given by the patient or immediate relative (first degree).
3- The meeting of SIRS criteria is due to an infection as per the treating physician.
4- Sepsis (ACCP/SCCM criteria):
   a- Clinically suspected infection by the treating physician or confirmed infection.
   b- 2 or more of the following: Temperature 38°C (100.4°F) or 36°C (96.8°F), Heart rate (HR) >90/min. Respiratory rate (RR) >20/ min or PaCO₂ <32mmHg. White blood cell count >1 2,000/mm³ or <4000/m³ or > 10% immature neutrophils.

5- Early sepsis (within 24 hours of development of the criteria of sepsis).
6- APACHE II score on admission not more than 25 (predicted mortality ≤50%).

Exclusion criteria:
1- Patients already on statin.
2- Pregnancy.
3- ALT >3 times above the upper limit of normal.
4- Elevated creatine phosphokinase (CPK) (>3 times the upper limit of normal).
5- Concurrent treatment with any of the following drugs: Daptomycin, fenofibrate, ketoconazole, triaconazole, amiodarone, clarithromycin, cyclosporine, erythromycin, nefazodone, niacin, protease inhibitors, telithromycin, verapamil, danazol and gemfibrozil.
6- History of allergy or intolerance to statins.
7- Greater than 16 hours after meeting inclusion criteria.
8- Use of 1 more doses of statins in the previous 4 weeks.
9- Clinical indication for treatment with statin during hospital admission (per treating physician).
10- Patients with severe sepsis, MOD or septic shock on admission.
11- APACHE II score on admission ≥3 5 (predicted mortality >80%).
12- Patients taken out from ICU against medical advice, whose investigations could not be done or lost and loss of patient follow-up, after discharge from ICU were also excluded from the study.

Patients who met the inclusion criteria were randomized into the study on the day of admission (if they are admitted because of sepsis) or the day they fulfilled the criteria of sepsis (if they acquired sepsis during their ICU stay) (Study day 1).

Study protocol:

Studied patients were divided into 2 equal groups (each consists of 25 patients) on a simple randomization pattern.
Statin group: 25 patients with early sepsis from a variety of etiologies and received statin therapy (Atorvastatin 80mg once daily either orally or via the nasogastric tube in the morning for 4 consecutive days) plus conventional sepsis ttt.

Control group: The other 25 patients served as control group received only conventional sepsis ttt which consists of treating or eliminating the source of infection, timely and appropriate usage of antimicrobial agents, hemodynamic optimization and other physiologic organ supportive measures.

All patients were followed-up for a total of 28 days (4 weeks) from study day 1 or till the day of discharge or demise.

Evaluation of patients: All included patients (in both groups) were subjected to the following:

1- Full clinical evaluation: Including history and physical examination with special emphasis on vital signs (BP, HR, Temperature and RR) and GCS; which were evaluated at the day of admission and then followed daily.

2- Laboratory investigations:
   - Routine Labs: CBC (complete blood count): Hemoglobin, Hematocrit, White blood cells and platelet count, Coagulation profile: PT, PC, INR and PTT, ABGs (arterial blood gases), LFTs: ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), BIL (bilirubin) and albumin, Kidney Function Tests: Na, K, Creatinine and Urea, CPK: Creatine phosphokinase.

   These routine Labs were withdrawn on study day 1 and subsequently thereafter every day until ICU discharge or demise or up to a total of 28 days.

   - Labs specific for our study: Were done at day 1 then at day 4 (after last dose of Atorvastatin).
     i- Lipid profile: Total cholesterol and triglycerides.
     ii- CRP (C-reactive protein): The CRP ELISA is based on the principle of a solid phase enzyme-linked immunosorbent assay. The assay utilizes a mouse monoclonal antibody against distinct determinants on CRP for immobilization on the microtiter wells and a goat anti-CRP antibody conjugated to horse-radish peroxidase (HRP) for detection [25].
     iii- PCT (Procalcitonin): We used the basic 3-day RIA protocol [26].
     iv- NOx (Nitric oxide metabolites): Ultrafilterate plasma or serum samples through a 10 or 30kDa molecular weight cut-off filter using commercially available centrifuge or microfuge ultra filtration device. The filters, supplied through Amicon or Millipore, should be pre-rinsed with Ultrapure water prior to ultra filtration of serum or plasma. Ultra filtration will reduce background absorbance due to the presence of hemoglobin and improve color formation using the Griess reagents. Assay for nitrate and/or nitrite using a maximum of 40 µl of the filtrate. The conversion of nitrate to nitrite require three hours for completion (i.e. spectrophotometric measurement of its stable decomposition products NO 3 and NO 2 [27]).

3- Microbiological studies: Including Pancultures (sputum, blood, urine or biological fluid according to clinical suspision) prior to antibiotic administration or after discontinuation of antibiotic for 48hrs.

4- Imaging studies: Required to identify the source of sepsis e.g. (ultrasound and chest X-ray).

5- Clinical data: Length of ICU stay, final outcome and need for organ supportive measures (Vasopressors, Mechanical ventilation and/or Hemodialysis) were reported for all patients until ICU discharge or demise or up to a total of 28 days.

6- Application of scoring systems: APACHE II ("Acute Physiology and Chronic Health Evaluation II") [28-29] score was evaluated on study day 1. APACHE II is a severity of disease classification system, one of several ICU scoring systems. After admission of a patient to an intensive care unit, an integer score from 0 to 71 is computed based on several measurements; higher scores imply a more severe disease and a higher risk of death.

The Sequential Organ Failure Assessment score, or just SOFA score [30] was evaluated on study day 1 and serially every day until ICU discharge or demise or up to a total of 28 days. It is one of several ICU scoring systems. It is a scoring system to determine the extent of a person’s organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems.

The statistical paragraph in material and methods:

Data were statistically described in terms of range, mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of
quantitative variables between the study groups was done using Student t test for independent samples when normally distributed and Mann Whitney U test for independent samples when not normally distributed. For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used in stead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 3 for Microsoft Windows.

Results

I- Demographic and clinical data:

Baseline clinical characteristics were comparable in both groups regarding age, gender, comorbid conditions (DM, HTN, CAD and renal impairment), source of sepsis, organism and antibiotic used.

Table (1): Demographic and clinical data of the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>10 (40%)</td>
<td>13 (52%)</td>
<td>0.571</td>
</tr>
<tr>
<td>Females</td>
<td>15 (60%)</td>
<td>12 (48%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.8±18.87</td>
<td>50.5±14.77</td>
<td>0.63</td>
</tr>
<tr>
<td>Comorbid conditions:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (40%)</td>
<td>14 (56%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (48%)</td>
<td>11 (44%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (40%)</td>
<td>8 (32%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>8 (32%)</td>
<td>4 (16%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Source of sepsis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>10 (40%)</td>
<td>9 (36%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Abdomen</td>
<td>4 (16%)</td>
<td>4 (16%)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>9 (36%)</td>
<td>10 (40%)</td>
<td></td>
</tr>
<tr>
<td>Organism:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grame +ve</td>
<td>8 (32%)</td>
<td>7 (28%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Grame –ve</td>
<td>16 (64%)</td>
<td>17 (68%)</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic used:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillins</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>8 (32%)</td>
<td>9 (36%)</td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td>13 (52%)</td>
<td>10 (40%)</td>
<td></td>
</tr>
<tr>
<td>Aminoglicosides</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Antifungal</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

II- Anti-inflammatory and pliotropic effect of statins determined by the following markers:

1- CRP level: The mean CRP level of both groups was compared at predetermined follow-up days (Study day 1 and 4). The mean level of CRP in day 1 was nearly the same between both groups which is elevated above normal range ($\leq 6mg/l$) (p value = 0.84). The mean level of CRP in day 4 decreased in both groups but mainly in statin group and this reduction was statistically significant between the two groups (p value = 0.007).

Table (2): Mean $\pm$ SD of C-reactive protein level at day 1 and day 4.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP 1 (mg/l)</td>
<td>55.9±32.8</td>
<td>54.1±26.6</td>
<td>0.84</td>
</tr>
<tr>
<td>CRP 4</td>
<td>33.3±22.9</td>
<td>51.9±24.1</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Fig. (1): CRP level at day 1 and day 4 in both groups.

2- PCT level: The mean PCT level of both groups was compared at predetermined follow-up days (Study day 1 and 4). The mean level of PCT in day 1 was nearly the same between both groups which is elevated above normal range ($\leq 0.5ng/ml$) (p value = 0.859). At day 4. The statin group exhibited significant decrease in PCT level than the control group (p value <0.001).

Table (3): Mean $\pm$ SD of PCL level at day 1 and day 4.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT1 (ng/ml)</td>
<td>0.64±0.16</td>
<td>0.64±0.17</td>
<td>0.859</td>
</tr>
<tr>
<td>PCT4</td>
<td>0.44±0.11</td>
<td>0.6±0.15</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Fig. (2): PCT level at day 1 and day 4 in both groups.
3- **NOx:** The mean level of NOx on admission was comparable between both groups which is elevated above normal range [≤29.6±8.9 (mu) M/L] \((p \text{ value} = 0.412)\). The mean NOx decreased in statin group but not in control group; but this reduction was not statistically significant \((p \text{ value} = 0.063)\).

| Table (4): Mean ± SD of NOx level at day 1 and day 4. |
|-----------------|-----------------|-----------------|
| Case            | Control         | \(p\text{-value}\) |
| NOx1 (mu) M/L   | 57.8±9.9        | 60±8.8          | 0.412 |
| NOx             | 56.4±10.3       | 61.5±8.5        | 0.063 |

Fig. (3): NOx level at day 1 and day 4 in both groups.

### III- Lipid lowering effect of atorvastatin:

Effect on total cholesterol (TC) level: The mean TC level of both groups was compared at predetermined follow-up days (Study day 1 and 4). The mean level of TC in day 1 was nearly the same between both groups (160.9±39.3 for the statin group versus 161.8±47.6 for the control group). The mean TC in day 4 decreased in statin group but not in control group; however this reduction was statistically insignificant \((p \text{ value} = 0.1)\).

| Table (5): Mean ± SD of TG level at day 1 and day 4. |
|-----------------|-----------------|-----------------|
| Case            | Control         | \(p\text{-value}\) |
| TC 1 (mg/dL)    | 160.9±39.3      | 161.8±47.6      | 0.9 |
| TC 4            | 145.3±32.3      | 161.9±46.2      | 0.1 |

Fig. (4): TG level at day 1 and day 4 in both groups.

### IV- Evaluation of severity of illness during ICU stay using SOFA scoring system:

The severity of illness was evaluated in each patient in the two groups at admission (Initial SOFA) and serially every day by using (SOFA) score then the Mean and Highest values were determined. When comparing the initial SOFA score between the two groups on admission; it showed no significant difference \((p \text{ value} = 0.87)\) i.e. both groups showed no significant difference in severity of illness on admission.

During the hospital course there was significant difference between both groups in favor of statin group, as indicated by Mean SOFA \((p\text{-value} = 0.038)\) and Highest SOFA \((p \text{ value} = 0.043)\).

| Table (6): Mean ± SD of initial SOFA, Mean SOFA and highest SOFA scores in both groups. |
|-----------------|-----------------|-----------------|
| Case            | Control         | \(p\text{-value}\) |
| Initial SOFA    | 3.6±0.96        | 3.6±0.77        | 0.87 |
| Mean SOFA       | 3.6±1.6         | 4.9±2.5         | 0.038 |
| Highest SOFA    | 5.4±2.7         | 7.6±4.7         | 0.043 |

Fig. (5): Initial SOFA, Mean SOFA and highest SOFA scores in both groups.

### V- Effect on clinical course, ICU stay and 28 day mortality:

The effect of statin on clinical course determined by the need for organ supportive measures as: (1) Need for vasopressors (V.C.), (2) Need for mechanical ventilation (M.V.) and (3) Need for acute hemodialysis (H.D.).

When comparing both groups regarding the need for organ supportive measures we found that the statin group exhibited significant decrease in need for vasopressors \((p \text{ value} = 0.001)\) and need for mechanical ventilation \((p \text{ value} = 0.044)\); on the other hand there is a nonsignificant decrease in the need for acute hemodialysis \((p \text{ value} = 0.5)\).
Effect of Statin Therapy in Early Sepsis

Table (7): The need for organ supportive measures.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for V.C.</td>
<td>5 (20%)</td>
<td>17 (68%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Need for M.V.</td>
<td>8 (32%)</td>
<td>15 (60%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Need for H.D.</td>
<td>3 (12%)</td>
<td>4 (16%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Fig. (6): The need for organ supportive measures.

Length of ICU stay: The mean length of stay in the ICU was 12±7.1 days for the statin group versus 13.9±4.2 days for the control group (p-value = 0.25); which signifies a statistically non-significant reduction in length of ICU stay.

Table (8): Length of ICU stay.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay (days)</td>
<td>12±7.1</td>
<td>13.9±4.2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

28 day mortality: The 28 day mortality was less in the statin group (40%) compared to the control group (56%); however this difference was not statistically significant (p value = 0.26).

Table (9): 28 day mortality in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 day mortality</td>
<td>10 (40%)</td>
<td>14 (56%)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

VI- Safety of statins:

The safety of statin can be assessed by serial measurement of liver and muscle enzymes during the period of drug administration.

A- Liver enzymes: Serial measurement of ALT and AST in statin and control groups showed a nonsignificant rise from baseline values (p value= 0. 12 8 & 0. 161 respectively).

Table (10): ALT and AST levels on admission and at day 4.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT adm</td>
<td>22.48±9.7</td>
<td>22.1±11.5</td>
<td>0.9</td>
</tr>
<tr>
<td>ALT day 4</td>
<td>28.36±29.7</td>
<td>33.2±17.3</td>
<td>0.128</td>
</tr>
<tr>
<td>AST adm</td>
<td>22.68±9.2</td>
<td>25.28±9.2</td>
<td>0.327</td>
</tr>
<tr>
<td>AST day 4</td>
<td>29.76±10.8</td>
<td>36.1±19.5</td>
<td>0.161</td>
</tr>
</tbody>
</table>

B- Muscle enzymes: Serial measurement of CPK in statin and control groups showed a non significant rise from baseline values (p-value = 0.9).

Table (11): CPK level on admission and at day 4.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPK adm</td>
<td>107.2±61.2</td>
<td>103.5±53.9</td>
<td>0.8</td>
</tr>
<tr>
<td>CPK day 4</td>
<td>107.5±48.8</td>
<td>107.4±60.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Discussion

Sepsis is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individual. HMG-CoA reductase inhibitors are potentially powerful inhibitors of the inflammatory process [31]. The mechanism by which statins modulate the immune response is regarded as lipid independent as they are not related to lowering LDL cholesterol.

We had examined the anti-inflammatory effect of statins in humans as guided by measuring serum levels of CRP and PCT at study day 1 and 4 which reflects the effect of statins on drivers of sepsis (e.g. IL6). We had found that; the mean level of CRP and PCT in day 1 was nearly the same between both groups which is elevated above normal range (≤6mg/L and ≤0.5ng/ml respectively), this was explained by sepsis. The mean level CRP in day 4 decreased in both groups but was lower in statin group as compared to control group and this reduction was statistically significant between the two groups (p value = 0.007). Also, the statin group exhibit significant decrease in PCT level than the control group at day 4 (p value <0.001).

In concordance to our study Macin SMM, et al., 2005 had demonstrated in a randomized controlled trial (RCT) [32] that patients with acute coronary syndrome treated with atorvastatin 40mg/day had a rapid reduction in CRP (a mean of 4 days after initiation of treatment) compared with placebo. Atorvastatin 40mg/day produced 32% more effect than equipotent doses of fluvastatin, lovastatin, pravastatin, or simvastatin in reducing CRP levels in patients with coronary heart disease.

A double-blinded, placebo-controlled, randomized study by Chello M, et al., 2006 demonstrated that atorvastatin (20mg/day) for 3 weeks before surgery significantly reduced IL-6 (therefore the CRP) and IL-8 release and neutrophil adhesion to the venous endothelium in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass [33].
In inflammatory conditions other than ischemic heart disease, statins have been shown to improve disease activity. For example, the trial of atorvastatin (40mg/day) in 116 patients with active rheumatoid arthritis (TARA) [34] demonstrated a significant improvement in clinical disease activity score. CRP and erythrocyte sedimentation rate declined by 50% and 28%, respectively, in the atorvastatin group compared with the placebo group.

These studies, therefore, indicate that statins are effective in decreasing systemic and vascular inflammation in humans in vivo.

We also had examined the effect of statin on endothelial function as guided by measuring nitric oxide metabolites level and found that statins for the early treatment of sepsis can reduce serum level of nitric oxide metabolites (nitrite and nitrates) but the reduction was statistically insignificant as follows. The mean level of NOx on admission was comparable between both groups which is elevated above normal range (≤29.6±8.9 "μ" M/L), this was explained by sepsis. The mean NOx at day 4 decreased in statin group but not in control group. This reduction was not statistically significant and can be explained by action of Atorvastatin on endothelial cells (pleiotropic action of statin).

In concordance to our study, Ando H, et al. [35] stated (in his study conducted on mice with Lipopolysaccharide-induced sepsis) that pre-treatment with cerivastatin also reduced serum levels of NO, nitrite and nitrate at 8h.

Regarding the effect of short term high dose statin therapy on total cholesterol serum level we had found that, the mean level of total cholesterol level at day 1 was nearly the same between both groups (160.9±39.3 for the statin group versus 161.8±47.6 for the control group) and its mean level at day 4 decreased in statin group but not in control group which may indicates the presence of a relationship between the hypolipemic effects of atorvastatin and its immunomodulatory effects; however this reduction was statistically insignificant (p value = 0.1).

In concordance to our study was Steiner et al. [36] who had stated in a double-blind placebo-controlled parallel group study, 20 healthy men were treated with high-dose simvastatin (80mg/d) for 4 days before intravenous LPS challenge (20IU/kg Escherichia coli, equivalent to 2ng/kg) and concluded that treatment with 80mg simvastatin over the course of 4 days resulted in a significant reduction in serum cholesterol levels (4.4±0.3mmol/L versus 3.6±0.3mmol/L, p<0.05). Apart from that, no further changes were detectable.

In addition, we had examined the effect of early statin therapy on reducing the rate of severe sepsis and we demonstrated a reduction of the risk of development of severe sepsis as indicated by comparing SOFA score and clinical course during ICU stay as follows: When comparing the initial SOFA score between the two groups on admission; it showed no significant difference (p value = 0.87) i.e. both groups showed no significant difference in severity of illness on admission. During the hospital course there was significant difference between both groups in favor of statin group, as indicated by Mean SOFA (p-value = 0.038) and Highest SOFA (p value = 0.043).

In concordance to our study Almog YM, et al. [37] had conducted a prospective observational cohort study of 361 consecutive patients admitted with suspected or documented acute bacterial infection and noticed that severe sepsis developed in 19% of patients in the no pre-statin group compared with only 2.4% of the pre-statin group.

More recently, Hackam DG, et al. [38] had conducted a population-based analysis of patients aged ≥65 years in Ontario, Canada, over a 6-year period. This resulted in a large cohort of 69 168 patients with cardiovascular disease, of whom half (n=34 584) received a statin and half (n=34 584) did not. They found that patients receiving statins had a 19-25% lower incidence of sepsis, severe sepsis, or fatal sepsis than those in controls [hazard ratio, HR (95% CI) 0.81 (0.72-0.91), 0.83 (0.70-0.97) and 0.75 (0.61-0.93), respectively].

In relation to mortality, we found that a statistically nonsignificant reduction in 28 day mortality in statin group; The 28 day mortality was less in the statin group (40%) compared to the control group (56%); however this difference was not statistically significant (p value = 0.26).

Similarly, Majumdar SR, et al. [39] had found that statins are not associated with reduced mortality or need for admission to an ICU in patients with pneumonia and reports of benefit in sepsis may be a result of confounding variables {Of 3415 patients with pneumonia admitted to hospital, 624 (18%) died or were admitted to an intensive care unit. Statin users were less likely to die or be admitted to an intensive care unit than non-users [50/325 (15%) V 574/3090 (19%), odds ratio 0.80, p=0.15]. After more complete adjustment for confounding, however, the odds ratios changed from potential benefit (0.78, adjusted for age and sex) to potential
harm (1.10, fully adjusted including propensity scores, 95% confidence interval 0.76 to 1.60).

In contrast to our results was Donnino M, et al. [40] in a prospective observational study of 2036 patients with suspected infection attending the emergency department found that the 412 patients on statin therapy had a clinically and statistically significant reduction in mortality. Absolute mortality was 1.9% (95% CI 0.6-3.3%) in patients on statins when compared with 4.4% (95% CI 3.4-5.4%) in those not on statins. Multiple logistic regression was used to control for severity of illness and co-morbidities and the odds ratio of death for statin patients was 0.44 (0.20-0.94, \( p = 0.03 \)) [41].

Also, Kruger et al. [42] who conducted a retrospective cohort analysis on 438 patient requiring hospital care for an episode of bacteraemia found a significant reduction in all-cause hospital mortality (10.6% Vs 23.1%, \( p = 0.022 \)) and death attributable to bacteraemia (6.1% Vs 18.3%, \( p = 0.0014 \)) in patients who were receiving statin therapy at the time of bacteraemia (n=66). The reduction in all-cause hospital mortality (1.8% Vs 23.1%, \( p = 0.0002 \)) and death attributable to bacteraemia (1.8% Vs 18.3%, \( p = 0.0018 \)) was more pronounced in the patients who continued to receive statin therapy after the diagnosis of bacteraemia (n=56). Statin use prior to admission was associated with a reduced adjusted hospital mortality rate (odds ratio 0.39; 95% CI 0.17, 0.91, \( p = 0.029 \)) and continuing statin use after bacteraemia increased this effect (odds ratio 0.06; 95% CI 0.01, 0.44; \( p = 0.0056 \)).

This difference may be attributed to small size of the study population, or the short term treatment regimen.

Regarding the effect of early statin therapy on clinical course, when comparing both groups regarding the need for organ supportive measures we found that the statin group exhibited significant decrease in need for vasopressors (\( p = 0.001 \)) and need for mechanical ventilation (\( p = 0.044 \)); on the other hand there is a nonsignificant decrease in the need for acute hemodialysis (\( p = 0.5 \)).

We had examined the safety of short term high intensity Atorvastatin therapy in early sepsis in the form of elevations in liver enzymes (defined as ALT or AST >3x the upper limit of normal) and/or muscle enzymes (defined as creatine kinase elevation of >10x upper limit of normal with muscle-related symptoms) and found the following results. Serial measurement of ALT and AST in Statin and control groups showed a non significant rise from baseline values (\( p = 0.128 \) & 0.161 respectively). Also, Serial measurement of CPK in Statin and control groups showed a non significant rise from baseline values (\( p = 0.9 \)).

In concordance to our study was Serruys PW, et al. [43], Waters DD [44] and Newman CB, et al. [45] who stated that the incidence of hepatic enzyme elevation in patients treated with high-dose atorvastatin, simvastatin, or fluvastatin in major trials is 0.5-3%. High-dose atorvastatin likely has slightly higher rates as seen in the IDEAL trial and in a randomized head-to-head efficacy and safety trial against simvastatin [46]. Discontinuation or dose reduction of the offending statin usually results in prompt resolution of the enzyme elevations.

The incidence of myopathy and frank rhabdomyolysis in controlled clinical trials employing the use of high-dose statin therapy is rare. In nearly 12,000 patients encompassing over 40 trials of high-dose atorvastatin, there were only two cases of myopathy [44].

**Conclusion:**

The use of a short term high intensity atorvastatin therapy in patient with early sepsis seems to be safe and associated with promising effects on inflammatory cascade and endothelial function reflected clinically by its effect on clinical course and mortality from sepsis.

Prospective studies with greater number of patients will be required to study the effect of long-term statin therapy on early sepsis and to assess the impact of statin therapy on severe sepsis and septic shock.

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