Evaluation of the Effect of Statins on Post-Surgical Patients with Acute Kidney Injury

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ABSTRACT

Introduction: Acute kidney injury is the sudden and almost complete loss of renal function with reduced glomerular filtration rate, and it occurs whenever the kidneys are unable to excrete metabolic waste products.

Method: This randomized double-blinded clinical trial was performed in an intensive care unit (ICU) of a university educational hospital. After randomization with a random assigning table of numbers, patients were divided into two groups: an intervention group and a control group. The patients’ daily blood urea nitrogen and creatinine levels were measured and changes were recorded. The statin group received a tablet of atorvastatin 40 mg daily (Abidi Pharmacy Production). Moreover, patients’ baseline vital signs and changes in serum blood urea nitrogen, creatinine, mechanical ventilation requirement, need for dialysis, ICU stays, and mortality were recorded in both groups. SPSS version 20 software was used for data analysis. P value <0.05 was considered significant.

Results: The mean intubation time for the intervention and control groups was 4.44±1.8 and 3.46±2.02, respectively, and the mean mechanical ventilation time was 2.14±2.15 and 2.34±2.07 days, respectively. The mean ICU stay was 4.91±3.3 days for the intervention group and 4.67±2.67 days for the control group. Throughout the study duration, the mean dialysis requirement frequency was 4.66±1.2 times in the intervention group and 5.54±1.75 times in the control group. Two patients in the intervention group and three patients in the control group died. There was no statistically significant difference in mortality between the two groups (P >0.05).

Discussion and conclusion: The effects of statins on the different stages of acute kidney injury and its outcomes are yet challengeable, so we recommend conducting further studies with larger sample sizes.

Keywords: acute kidney injury, statins, outcome, intensive care unit

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INTRODUCTION

Acute kidney injury (AKI) occurs when the kidneys are unable to excrete metabolic waste products and do not have a natural function. Acute kidney injury is a sudden and almost complete loss of renal function with reduced glomerular filtration rate. There are three main reasons for AKI, including pre-renal, renal and post-renal disturbances. Decreased perfusion due to decreased blood volume or heart failure is one of the leading causes for pre-renal states. Transfusion reactions, nephrotoxicity, renal tubular injury, and infections are the most common intra-renal causes of AKI. Oliguria (urinary volume < 400 mL/day), hyperkalemia, uremia, and rises in creatinine (Cr) level occur in AKI. Several studies have been conducted for finding ways to reduce mortality and morbidity in acute renal failure patients, among which the use of statins is noteworthy. Cellular injury mechanisms in AKI include cellular adhesion, inflammatory cell infiltration, free radicals production and inflammatory cytokines. Statins can completely inhibit the release of inflammatory mediators by macrophages and monocytes. The outer medulla of the kidney is one of the susceptible areas to hypoxemia (1). Ischemia is the main reason for AKI in major surgeries or kidney transplant operations, in which statins can conserve kidneys by improving the perfusion of renal tubular tissue and increasing nitric oxide (2, 3).

Anti-inflammatory, vasodilatation and anticoagulation effects of statins are mediated by releasing nitric oxide from endothelial cells (4). Statins can reduce the incidence of AKI up to 1.3 times (5, 6). A mortality rate for AKI of about 60% has been reported (7, 8). This mortality rate requires rapid intervention in these patients. In a German study in mice, statin treatment led to a reduction in the incidence of AKI (9). In another study carried out in the USA on thousands of patients using statins, a reduction in the incidence of AKI in patients who underwent non-cardiac surgery was reported (10). In a meta-analysis performed in Germany, the preventive effects of statins have been established for heart diseases (11). Taking into account the studies that have established the effectiveness of statins in improving the status of these patients, we aimed to conduct the current study in this framework.

METHOD

After approval by the research committee of the Medical Faculty and ethical committee of Urmia University of Medical Sciences, 70 patients (calculated with power SSC software with p2=80%, p1= 20%, α=0.05 and 1-β=0.8) admitted to a university educational hospital following non-cardiac surgery (abdominal surgery: cholecystectomy) and diagnosed with AKI without need for blood transfusion were included. After meeting the inclusion criteria and fulfilling a written informed consent, the study was started. A double-blind randomized controlled trial (RCT) design was used. The subjects were assigned to one of two groups – an intervention group or a control group – using a computer-generated table of random numbers. All nurses, residents, patients, and caregivers were blinded to treatment during the study. The inclusion criteria were: 1) to be diagnosed with AKI after a non-cardiac surgical intervention; 2) age of 25 < and ≤70 years old; 3) physical status of <ASA III; 4) lack of using the nephrotoxic drugs; and 5) absence of significant conditions in patients (DIC, thrombosis, etc.). The exclusion criteria were: 1) patients with renal failure due to urinary tract obstruction; and 2) presence of liver dysfunction or failure.

After admission, patients underwent non-cardiac surgery in ICU, and routine tests were performed. The intervention group received a daily dose of atorvastatin 40 mg (Abidi Pharmacy Production) for two weeks, while the control group received a placebo. The patients’ baseline vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature were recorded. Also, serum levels of BUN and Cr were measured daily. Patients in the two groups were matched by age at the date of admission. Proper Folley catheter was fixed in all the patients and the collected data were given to a relevant nephrologist, who was blinded to the patients’ assignment. The pre-provided checklist was completed and data were subsequently analyzed with SPSS v.20, while P value <0.05 was considered significant. At first, data were analyzed for normality via using the Kolmogorov-Smirnov test. Accordingly, parametric or non-parametric tests were recruited for appropriate ones. An independent sample t-test was used for
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Comparing groups based on baseline vital sign and ICU stays. Once the t-test repeated, Ancova was used for comparing two groups at the start and end of the intervention and before and after the intervention. The $\chi^2$ test was used to compare the groups based on mechanical ventilation requirement and mortality.

The definition of AKI in this study was according to at least 25% increase in serum creatinine from patients’ baseline levels (12).

RESULTS

Seventy patients were assessed in this study. Thirty-five of them received statins (intervention group) and thirty-five (control group) placebo. Seventeen patients in the intervention group were males (48.6%) and the rest were females. Participants’ demographic and baseline characteristics are shown in Table 1.

Concurrent effect of treatment time and group for BUN was not significant according to the presented means ($P=0.15$) (Figure 2). Concurrent effect of treatment time and group for serum creatinine was not significant according to the presented means ($P=0.07$) (Figure 3).

The mean intubation time was similar between the intervention group and the control group ($P=0.25$). Also, there was no significant difference between the two groups regarding the mechanical ventilation time ($P=0.69$) and the duration of ICU stay ($P=0.78$) (Table 2).

### TABLE 1. The patients’ demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (Mean ±SD)</th>
<th>Measured value (Mean ±SD)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.08 ±14</td>
<td>57.20 ±12.22</td>
<td>0.93</td>
</tr>
<tr>
<td>Height</td>
<td>168±3.14</td>
<td>167.78±4.1</td>
<td>0.94</td>
</tr>
<tr>
<td>Weight</td>
<td>78.19±8.7</td>
<td>80.31±6.9</td>
<td>0.89</td>
</tr>
<tr>
<td>BMI</td>
<td>27.72±2.1</td>
<td>28.47±1.87</td>
<td>0.86</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>8.29±2.12</td>
<td>8.34±2.18</td>
<td>0.91</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>114±14.3</td>
<td>109.5±12.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>93.7±8.7</td>
<td>95.1±7.4</td>
<td>0.88</td>
</tr>
<tr>
<td>(Number (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 17 (48.6%) Male: 17 (48.6%)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>5 (14.28%)</td>
<td>4 (11.42%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (22.85%)</td>
<td>9 (25.71%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (40%)</td>
<td>14 (27.45%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (22.85%)</td>
<td>8 (22.85%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Diagram of inclusion and randomization of the subjects
The average frequency of need for dialysis was 4.66 ± 1.2 in the intervention group and 5.54 ± 1.75 in the control group; however, the difference was not meaningful (P=0.22).

Two (5.7%) of the 35 patients in the intervention group expired and 33 patients (94.3%) were discharged after recovery. Moreover, three patients (8.6%) among the 35 patients of the control group expired and 32 patients (91.4%) were discharged after recovery. Based on Fisher’s exact test, there was no significant difference in mortality between the two groups in the current study (P=0.5). In the intervention group, two subjects died: one from sepsis, and the other one from ARDS. In the control group, two patients died from sepsis and one from VTE.

**DISCUSSION AND CONCLUSION**

**A**KI is the sudden and almost complete loss of renal function with reduced glomerular filtration rate, and it occurs whenever the kidneys are unable to excrete metabolism waste products. Several studies have been conducted for finding a way to reduce mortality and morbidity in patients with AKI, among which statin use is notable (1). It has been shown that statins can lead to GFR improvement (2, 3).

The current study was conducted to investigate the effect of statins on the outcome of admitted patients with AKI following non-cardiac surgery in ICU. The results of this double-blind RCT revealed no statistically significant difference in mean intubation period, mean mechanical ventilation period, mean ICU stay length, mean dialysis requirement frequency, and mean mortality and morbidity between the two groups (P >0.05).

A few studies have investigated the effect of statins on AKI. In an animal study carried out in 2002, Gueler et al. (9) reported that statins conserve renal tissue against ischemic and injuries due to decreased perfusion, and since statins had led to a 40% decrease in Cr level elevation in their study, they recommended using these drugs in order to reduce the severity of AKI. In 2010, Argalious et al. (10) evaluated the relation between statins and AKI in non-cardiac surgeries and stated that there was no relationship between statins and AKI, mortality and frequency of peritoneal dialysis after non-cardiac surgery. In contrast to Gueler et al.’s study on animals (9), our study conducted on patients undergoing non-cardiac surgery showed no significant difference in outcomes between the two study groups (P >0.05). Gueler et al. (9) reported that a group of a mice with the lack of receiving the statins had a higher decline in the glomerular filtration rate. Despite the small sample size of our study, it confirmed the findings of Argalious et al. (10), which revealed that there was no relation between statins, AKI and their outcomes, but there was a significant difference between the types of dialysis (hemodialysis against peritoneal dialysis).

In a meta-analysis conducted by Van Lier et al. in 2011 (11) it has been stated that the effect
of statins was much more than they expected. In their study, they referred to their previous studies with some specific inclusion criteria. Their findings showed that the anti-inflammatory effects of statins can be mediated by decreasing the level of CRP and IL-6. Also, statins can lead to a decline in neutrophil adherence to endothelial cells and neutrophil apoptosis. For achieving this, they used statins 30 days before surgery, although Yasuda et al. (13) had previously stated, in 2006, that simvastatin reduced TNF-α and improved renal oxygenation, thus leading to a decrease in mortality from septic shock with AKI. However, we found no significant difference between mortality and expected outcomes in the two groups.

In their 10-year longitudinal retrospective study on 98,939 patients undergoing abdominal, cardiovascular and thoracic surgery, Bruneli et al. (14) evaluated the relation between AKI and statins and reported that the risk of AKI after surgery declined in patients with statin intakes and this relationship was stronger in patients with vascular surgery and weaker in those with cardiac surgery. One year before them, Molnar et al. (15) published the results of their 14-year study in Canada and reported that 32% of their patients used statins before surgery, with 16% of them having a reduced incidence of AKI, 17% a reduced emergent dialysis requirement and 21% a reduced mortality rate.

In contrast to the studies of Bruneli (14) and Molnar et al. (15), our study showed no difference between investigating outcomes of the two groups. Moreover, our sample size was limited in comparison with that in their studies, and that was one limitation in the current study. Singh et al. (16) published a meta-analysis in 2012 in which they investigated 17 studies with 47,080 patients and stated that the group who used statin before heart surgery, notwithstanding the type, had a lower mortality rate. As compared to the study of Singh et al. (16), our study was conducted in a shorter time interval (throughout the year of 2015) on non-cardiac surgery patients. This study confirms the results from some studies (10) in this context and is not in accordance with some others. A notable point in our study is that we assessed the effect of post-operative statins and this is different from previous studies on human models since they all investigated the effect of pre-operative statin use.

Finally, according to the results obtained in the previous studies as well as in the current study (regardless of similarities and differences), the effect of statins on different stages of AKI and their outcomes is yet debatable and further studies with larger sample sizes are needed.

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**References**


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