Investigating the Effect of Atorvastatin in Preventing Ventilator Associated Pneumonia among Patients with Cerebral Ischemia Hospitalized in ICU in Imam Khomeini Hospital in Urmia City

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Abstract

Introduction: ventilator associated pneumonia is one of the main reasons of death in patients under ventilator, especially those with impaired consciousness hospitalized in intensive care unit (ICU). Having anti-apoptotic, antioxidant, and immunomodulatory effects, atorvastatin can be effective in preventing pneumonia in patients with stroke who are under ventilator, while it is also prescribed to reduce cholesterol and accelerate recovery process in ischemia cases. The present study aims at investigating the preventive effects of atorvastatin on ventilator associated pneumonia among patients who suffer from stroke and are under the ventilator. Methodologies in the present study, 60 patients hospitalized in ICU unit under ventilator following an ischemic attack were divided to two groups of 30. The treatment group received a daily 40-mg dose of atorvastatin, while the control group didn't. Then the occurrence of pneumonia was extracted for both groups during at least 14 days of hospitalization, and the results were analyzed using SPSS20 software. Results the results of the study indicated that the amount of occurrence of pneumonia among patients treated by 40 mg atorvastatin was significantly lower than the patients in control group. Therefore prescribing daily 40 mg atorvastatin for the patients with ischemia in ICU unit who are incubated and are under mechanical ventilation would reduce ventilator associated pneumonia significantly. Conclusion atorvastatin has a significant reducing effect on occurrence of ventilator associated pneumonia in patients suffering from ischemic stroke in ICU unit, who are incubated and under mechanical ventilation, which will be proved clinically in the present study.

Keywords: ventilator associated pneumonia, Cerebral ischemia, Atorvastatin.

Introduction

Cerebral ischemia is the reduction of brain metabolites as a result of decreased blood flow, leading to decreased oxygen supply and hence the death of brain tissue or stroke(1). Cerebral ischemia is one of the biggest problems in the world, the main reason of which is stroke which is the third reason of deaths in developed countries after myocardial infarction and cancer. Cerebral ischemia causes several problems including motor disorders, sensory and sight disorders, aphasia, behavioral disorders particularly spatial learning disorder (2-4). Patients with ischemia usually suffer from depression, functional disorders, feeling decreased contribution in life, and lack of sufficient social support (5). Epidemiological investigations indicate that strokes are associated with gender and their occurrence in men is higher than women. It is especially obvious in women after starting menopause (6,7). More than 75% of the strokes occur in people above 65 years old, which along with the other accompanied diseases increase
disability, hospitalization, and death risk (8). Although its occurrence has decreased over the past two decades, its overall occurrence has increased due to the aging of the population of the world (9). According to the report by world forum for stroke one out of every six people suffer from stroke in their lifetime (10). Generally, strokes are of two types, Hemorrhagic strokes and ischemic strokes, and the latter is the most common type of stroke (11).

Cellular death occurs as a result of occlusion and blood supply constraint and consequently lack of oxygen required by the neurons (12). During ischemia the amount of oxygen and ATP of the brain reduces, and consequently the degree of free radicals removal reduces; as a result, free radicals and lactate from anaerobic respiration increase, leading to acidosis and cellular death (13). Reperfusion injuries are those injuries created because of the return of blood flow after a period of ischemia.

The lack of oxygen and nutrition leads to a special situation. As a result, return of the blood flow can lead to inflammation and oxidative lesions resulted from oxidative stress (14). There is evidence for effectiveness of medicine treatment in relative improvement of the lesions caused by brain injuries (15). Using antioxidants can lower the cellular mortalities by reducing cellular injuries (16,17). Atorvastatin is among these antioxidants. Atorvastatin is a member of statins family. They are the most important fat reducing drugs and are known as 3-hydroxy 3-methyl glutaryl A-reductase coenzyme inhibitors as well (18).

Statins reduce the cholesterol levels in body by blocking the synthesis of mevalonate. Furthermore, statins improve the function of vascular endothelial, inhibit the progress of sclerotic plaques and have anti-inflammatory effects (19). Recently there have been a wide range of studies performed on the anti-inflammatory, antioxidant, and immunomodulatory effects of this family, and the positive results of these studies have increased the tendency to use statins as a preventing factor helping treatment of infectious diseases, immunology system disorders, and even helping quicker recovery of ischemic disorders (20-22). Atorvastatin decreases the level of inflammatory cytokines like interleukins 6, 8, 1B, and TNF-α; and chemokines like CCL5, CCL2, MMP9, and NF-KB, and thereby reduces the accumulation of type T immunological cells (23). Due to the antioxidant and anti-inflammatory effects, statins can help quicker reperfusion following ischemic events (24-26).

Several studies and papers have investigated the effects of statins, particularly atorvastatin and simvastatin in patients connected to ventilator, in terms of occurrence of VAP.

Atorvastatin also has shown a neuroprotective effect during the periods before and after ischemia. It applies its effect through various mechanisms. Mostly, this effect is through regulation of synthesis of nitric oxide (NO) in endothelial cells, leading to increased capillary blood flow (22, 24, 27).

Auxiliary ventilation aims at supplying oxygen required by the patient to breathe, which is used until the primary background disease is better and the patient can breathe automatically (28). Ventilator associated pneumonia (VAP) is one of the main reasons of death of patients who are under ventilator, particularly those in ICU (20). This type of pneumonia generally occurs in patients incubated and connected to ventilator because of decreased level of consciousness and the consequent apnea, or failure of respiratory centers or probable breathing stop (21).

This occurs usually 48 hours after connecting ventilator to the patient (29). 9-27% of intubation cases suffer from this problem, while the mortality caused by ventilator pneumonia is 25-50% (30,31). In this situation the patient needs longer ventilation, longer period to stay in ICU, more antibiotics, and hence higher financial costs imposed on health system (32, 33). Therefore VAP is a main problem among the patients in ICU who are connected to ventilator (21).

In the present study, the primary purpose is to investigate VAP occurrence in patients with stroke who are connected to ventilator, while investigating other effects and improvement of reperfusion in such patients are the secondary purposes. The multiple effects of atorvastatin on treatment of the
problems associated with ischemia will be investigated both individually and totally in the patients with ischemic strokes.

**Methodology**

The present study is experimental in nature. 60 individuals who have been selected according to inclusion and exclusion criteria, were divided into two groups of 30. The treatment group received a daily dose of 40 mg atorvastatin, while the control group didn’t. The other prescribed medicines were the same in both groups, and the treatment and control group were matched.

**The inclusion Criteria According to Similar Studies**

- Age of 18-80 years for both genders
- Being hospitalized in ICU with cerebral ischemia
- Need to mechanical ventilation and intubation
- The minimum time of intubation and mechanical ventilation > 48 hours
- informed consent for participation in the study

**The Exclusion Criteria**

- Occurring pneumonia before or during the time of hospitalization
- Recently receiving statin with effective dose and period within the last 6 months
- Chronic liver disease or active liver disease
- Increased level of CPK more than 3 times of the upper level
- Malnutrition
- Pregnancy
- Dissatisfaction to continue treatment

All the patients who have been in hospital for cerebral ischemia diagnosed by neurologist during the past 2 months and were between 18 to 80 years old, were selected from both genders; and after being informed of the program and taking consent from them they were placed into two groups, treatment and control.

The treatment group received a nightly dose of 40 mg atorvastatin through PO or feeding tube during the period being in hospital at least for 48 hours; the occurrence of pneumonia was diagnosed by an infectious disease specialist and the crude amount of pneumonia occurrence was recorded for a 2-month interval. The obtained data was collected in the form of checklists and the collected information was analyzed using SPSS20.

**Results**

In the present study, in order to investigate the effects of atorvastatin following ischemia-reperfusion among the patients who are under ventilator in ICU, 60 patients, 30 men and 30 women, were selected and matched so that in each group there were 15 men and 15 women.

The control group received the normal treatment similar to the treatment group except for atorvastatin. The treatment or case group received a daily dose of 40 mg atorvastatin along with the normal treatment. Then each patient was observed during the days in hospital either in ICU or the hospital ward by the infectious disease specialist for maximum 14 days. The infection or non-infection by pneumonia for each individual was recorded in the relevant checklist after being confirmed by the infectious specialist.

The age average in the control group was 74.83 with the standard deviation 9.05, while the age average in treatment group was 69.76 with the standard deviation of 10.34. This difference is not significant statistically (p-value=0.14).

Both group, treatment and control included 30 patients; 15 male patients and 15 female patients were selected from each group. 7 patients of the patients receiving 40 mg daily dose of atorvastatin got pneumonia while they were in hospital. Among the patients who didn’t received atorvastatin, 15 patients got pneumonia while they were in hospital.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pneumonia (no)</th>
<th>Pneumonia (yes)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin (no)</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Atorvastatin (yes)</td>
<td>23</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>22</td>
<td>60</td>
</tr>
</tbody>
</table>
In the above table, the first row indicates that among the 30 patients of control group who have not received atorvastatin, 15 patients got pneumonia.

The second row indicates that among 30 patients of the treatment group who received atorvastatin, 23 patients didn't get pneumonia and 7 patients got this disease.

To investigate the relationship between using atorvastatin and pneumonia occurrence we used Chi-square test. The results of this test indicate a significant relationship between using atorvastatin and pneumonia occurrence (p-value=0.032).

Chart 1: Comparing atorvastatin receivers in case group and the control group who didn't receive atorvastatin

Table 2: Cross-sectional frequency distribution, the relationship between gender and pneumonia occurrence among all the patients in 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pneumonia (no)</th>
<th>Pneumonia (yes)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>22</td>
<td>60</td>
</tr>
</tbody>
</table>

According to table 2, 16 of 30 female patients got pneumonia, while only 6 of 30 male patients got pneumonia. Due to the results obtained from the Chi-square test there is a significant relationship between gender and pneumonia occurrence (p-value=0.007).

Table 3: Cross-sectional frequency distribution, the relationship between gender and pneumonia occurrence in treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pneumonia (no)</th>
<th>Pneumonia (yes)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>7</td>
<td>30</td>
</tr>
</tbody>
</table>

It is observed from the table 3 that 7 of 15 female patients got pneumonia, while no male patient got pneumonia. Regarding the results obtained from Fisher's exact test there is a significant relationship between gender and pneumonia occurrence in treatment group (p-value=0.006).

Table 4: Cross-sectional frequency distribution, the relationship between gender and pneumonia occurrence in control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pneumonia (no)</th>
<th>Pneumonia (yes)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

Also, 9 of 15 female patients got pneumonia, while 6 of 15 male patients got pneumonia; however this difference was not significant statistically. According to the results of Chi-square test there is no significant relationship between gender and pneumonia occurrence.
difference in control group (p-value=0.273). Finally, it can be concluded from the above investigations that atorvastatin is more effective in men than women.

**Discussion**

Ventilator associated pneumonia is a main cause of death among patients who are under ventilator, especially those with impaired consciousness in ICU. It leads to increased need to ventilator, increased mortalities among the ICU patients and other patients under ventilator, and consequently increased financial costs imposed on health system.

Due to the efforts that have been done to prevent ventilator associated pneumonia and to investigate different effects of statins and particularly atorvastatin in preventing pneumonia, we investigated the effect of atorvastatin in preventing ventilator associated pneumonia in patients who are hospitalized in ICU for cerebral ischemia and are intubated under mechanical ventilator.

Statins improve bronchial performance in lungs, prevent the progress of emphysema, reduce inflammatory cells, and hence reduce inflammatory cytokines such as SRP, Interleukin 6&8, and TNF-α (34). In animal models, statins reduce leukocytes accumulation during infection, and reduce transplant rejection in heart transplant patients, and reduce inflammatory in autoimmune diseases (35).

Liu Chunyan et al (36) found that pneumonia occurrence is significantly lower in atorvastatin group than placebo group; in their study 42% of the case group got pneumonia while in control group 59% of the patients got pneumonia. They concluded that atorvastatin has a preventive effect on pneumonia occurrence. Clark et al (37) investigated the effect of statins on mortality of patients with VAP.

On the 28th day, following diagnosis of pneumonia in two groups suffering from VAP who were treated by simvastatin and placebo, mortality was 15.2% in simvastatin group and 21.2% in control group. These findings confirmed the above hypothesis and indicated the reduced risk of pneumonia in simvastatin group as well as reduced mortality in this group.

VAP is a subsequent of brain stroke, and lung disease background, more severe stroke, and hemorrhagic type of stroke increase the probability of it as well as length of hospitalization (38,39).

However, statins do not significantly vary the mortality and length of hospitalization of the patients with community-acquired pneumonia (40). Also, a daily 20-mg dose of simvastatin does not decrease the length of hospitalization among patients suffering from community-acquired pneumonia and doesn't significantly decrease the amount of inflammatory cytokines (interleukins 6 &10, CRP, and TNF-α) (41).

It was found in a futuristic study that mortality and hospitalization length of influenza patients for statins consumers and those who don't consume statins were obtained 3.5% and 5.2% respectively, which indicates a 27% decrease among patients who consume statins (42). Statins may decrease the mortalities caused by pneumonia, but it is not clear that whether to start prescription of statins at the time of diagnosis is helpful or not (43).

In another futuristic study it was found that continuing statin consumption can decrease the 30-day mortality for the patients with VAP who had already used it (44). However, L Papazian et al found that simvastatin prescription as an adjunct treatment does not improve 28-day survival of patients with VAP (45). It was found in a retrospective study that high power statins not only don't improve community-acquired pneumonia, but also may increase mortality (46).

Using clinical treatment in this study, we conclude that atorvastatin with a daily dose of 40 mg can decrease ventilator associated pneumonia and mortality for the patients hospitalized in ICU unit who are intubated under mechanical ventilation and are exposed to the risk of ventilator associated pneumonia. Atorvastatin also seems to have other positive effects like decreasing blood cholesterol level, neuroprotective and antioxidant effects as well as strengthening immune system. However, due to different findings in different studies, it is recommended that further investigations be done.
Reference

Cerebrolysin effects on neurological outcomes and cerebral blood flow in acute ischemic stroke. Neuropsychiatric Disease and Treatment. 10 (3): 2299-2306.


