Simvastatin administration on rabbit with knee immobilization have higher chondrocyte number and lower serum cartilage oligomeric matrix protein level compared without simvastatin administration

Sumadi Ik,1 Suyasa Ik,2 Siki Kawiyana Ik2

ABSTRACT

Prolong Joint immobilization can lead cartilage damage. One of mechanism is release of proteolitic enzim such as MMP3. Simvastatin has capacity to become anti proteolitic enzyme which is released by chondrocyte. Oral simvastatin administration on joint immobilization can prevent cartilage damage monitored by lower serum COMP level and higher chondrocyte number on cartilage compared without simvastatin administration. This research was Randomized post-test only group design consists of 38 female rabbit as subject. All of rabbit’s knee were immobilized by cast and divided into 2 group. First group with no simvastatin administration and second group with oral simvastatin administration 20mg/kg/day for 6 week. Chondrocyte number on cartilage and serum COMP level was measured at the end of the six weeks study. Statistic analysis showed higher chondrocyte number and lower serum COMP level of rabbit’s knee with simvastatin administration compared with group rabbit with no simvastatin administration. Independent t-test analysis showed that difference were significant, with serum COMP p = 0.000 (p < 0.05) and chondrocyte number p = 0.000 (p < 0.05). Oral simvastatin administration on rabbit with knee joint immobilization have higher chondrocyte number and lower serum COMP level compared with group with no simvastatin administration.

Keywords: Immobilization, simvastatin, chondrocyte, COMP

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ABSTRAK

Immobilisasi sendi dalam waktu lama menyebabkan terjadinya kerusakan cartilage melalui pembentukan enzim proteolitic yaitu MMP3. Simvastatin memiliki efek anti proteolitic dengan cara menghambat pembentukan MMP3 oleh Kondrosit. Pemberian simvastatin pada immobilisasi sendi diharapkan dapat mengurangi tejadinya kerusakan cartilage yang ditandai dengan kadar serum COMP yang lebih rendah dan jumlah Kondrosit yang lebih banyak dibandingkan tanpa pemberian simvastatin. Penelitian eksperimental Randomized post-test only group design dengan sampel 38 ekor kelinci. Semua kelinci diimobilisasi sendi lututnya dengan cast, kemudian dibagi menjadi 2 kelompok. Kelompok pertama tidak diberikan simvastatin, kelompok kedua diberikan simvastatin tablet 20 mg/kg bb/hari selama 6 minggu. Pada minggu ke-ena, untuk menilai efek perlakuan diperlakukan kadar serum COMP dan jumlah kondrosit pada cartilage. Analisis statistik didapatkan kadar kerata serum COMP pada kelinci dengan pemberian simvastatin lebih rendah dan jumlah kerata kondrosit pada cartilage kelinci lebih banyak dibandingkan tanpa pemberian simvastatin, pada uji independent t-test didapatkan perbedaan yangbmkakna dengan kadar serum COMP p = 0,000 (p < 0,05) dan jumlah chondrosite p = 0,000 (p < 0,05). Pemberian simvastatin oral pada kelinci yang diimobilisasi sendi lututnya memiliki jumlah kondrosit yang lebih banyak dan kadar serum COMP yang lebih rendah dibandingkan tanpa pemberian simvastatin

Kata kunci: Immobilisasi, kerusakan cartilage, simvastatin, kondrosit, COMP

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INTRODUCTION

Risk factors for osteoarthritis (OA) is not just purely because of the aging process but could occur because of medical action, particularly in the field of orthopedics. One risk factor is the immobilization of the joints. Until now immobilization of the joints is carried to the treatment of patients with musculoskeletal injuries. Immobilizing the joint is still often done in cases of fractures are treated conservatively.

Immobilizing cause various disorders of the cartilage, for example, affects the thickness of cartilage, the number of chondrocytes, decreased levels of proteoglycan (PG) and changes in levels of kolagen. Recent research also shows, the joint immobilization proteolitic the process since the increase in MMP1 and MMP3 on cartilage tibia immobilized for 6 weeks.

Statins are competitive inhibitors of hydroxymethylglutaryl (HMG-CoA) reductase and is widely used to decrease serum lipid levels by inhibiting cholesterol formation chain. Simvastatin is a HMG-CoA reductase inhibitor, lowers worsening OA by reducing the expression of MMP3 in the joint cartilage. Simvastatin reduced mRNA levels of MMP2 and MMP3. COMP is one of the best OA biomarker, produced by chondrocytes and sinovite and can serve as a good marker for cartilage degradation or turnover synovium or both.

MATERIAL AND METHODS

This research was experimental study with randomized post-test only group design consists of 38 female rats as subject. All of knee rabbit were immobilized by cast and divided into 2 group. First group with no simvastatin administration second group with oral simvastatin administration 20 mg/kb bw/day for 6 week. At the end of the six week serum COMP level and chondrocyte number on cartilage measured.

RESULT

Descriptive data analysis data shown in the Table 1. Mean serum COMP level with simvastatin administration is 7.94 (SD 3.7013) much more lower compared with group without simvastatin administration 29.92 (SD 24.1971). Mean chondrosite number on cartilage knee rabbit with simvastatin administration is more higher 75.10 (SD6.4108) compared with group without simvastatin administration.

After being tested for normality by the Shapiro Wilk test, both groups were at normal distribution where the value of p > 0.05, seen in Table 2. Because both group have normal distribution parametric test was conducted by using independent t-test to determine the significance of the mean differences between the two groups.

Table 1 Mean Serum COMP Level and Chodrocyte Number on Both Group

<table>
<thead>
<tr>
<th>Variabel</th>
<th>Group</th>
<th>Case simvastatin (+) (n = 19) (Mean ± SD)</th>
<th>Control Simvastatin (-) (n = 19) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum COMP Level</td>
<td></td>
<td>7.94 (SD3.7013)</td>
<td>29.92 (SD24.1971)</td>
</tr>
<tr>
<td>Chondrocyte Number</td>
<td></td>
<td>75.10 (SD6.4108)</td>
<td>53.57 (SD5.4295)</td>
</tr>
</tbody>
</table>

Table 2 Normality Test Using Shapiro-wilk Test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>P</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum COMP level</td>
<td>Case</td>
<td>19</td>
<td>0.248</td>
<td>Normal</td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrocyte number</td>
<td>Case</td>
<td>19</td>
<td>0.072</td>
<td>Normal</td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Inferensial Test Using Independent T-Test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Case Simvastatin (+) (n = 19)</th>
<th>Control Simvastatin (-) (n = 19)</th>
<th>Mean</th>
<th>95% CI</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum COMP level</td>
<td></td>
<td>7.94 ± 3.7013</td>
<td>29.92 ± 24.1971</td>
<td>-21.979</td>
<td>-33.368 to (-10.590)</td>
<td>0.000</td>
</tr>
<tr>
<td>Chondrocyte number</td>
<td></td>
<td>75.10 ± 6.4108</td>
<td>53.57 ± 5.4295</td>
<td>21.526</td>
<td>17.617 to 25,435</td>
<td>0.000</td>
</tr>
</tbody>
</table>
In inferential test with independent t-test (Table 3) showed that the serum levels of COMP is lower in the case group compared with the control group, and the difference between case and control group was statistically significant with p = 0.000 (p < 0.05), while the number of chondrocytes in the case group more than the control group, and the difference between case and control group was statistically significant with p = 0.000 (p < 0.05).

DISCUSSION

The analysis showed administration of simvastatin in the rabbit immobilized knee have more number of chondrocytes and lower serum levels of COMP than without administration of simvastatin, and significantly mean difference significant.

On research eksperimental study, repair process of joint cartilage degeneration during immobilization, including chondrocyte proliferation and synthesis proteoglycan, has been shown to be activated during the immobilization. Chondrocytes secreting enzymes called metalloproteinases (collagenases, gelatinases, and stromelysin), which regulates the degree of degradation. Degradation of proteoglycans followed by increased synthesis of proteoglycans, which are then integrated in tissue. Immobilization causes the degeneration of cartilage which one character is a decrease in the number of chondrocyte. Simvastatin may inhibit the degeneration of cartilage by preventing the expression of MMP3 on cartilage. MMP3 is one of the known protease responsible for the generation of cartilage. Some studies suggest that the metabolism of the chondrocytes which is modulated by statins by reducing the prenylation of the main molecules that control of enzymes that degrade collagen.

Serum levels of COMP can be used for a marker of cartilage damage and can be used to determine the therapeutic response of cartilage. Aktaş showed simvastatin can decreased cartilage degeneration by reduced protease activity which is released by chondrocyte. Acharya showed administration of drugs that can inhibit the degradation of COMP can reduce the occurrence of arthritis. Simvastatin can be given as prevention of cartilage degradation as the effects of immobilization. Simvastatin is a drug that is cheap, safe, and easy administration. This result is consistent with the research hypothesis that serum levels of COMP rabbits immobilized with a cast given oral simvastatin lower than rabbits immobilized with a cast without giving simvastatin.

REFERENCES


CONCLUSION

From the data analysis has been done in this study, some conclusions can be obtained as follows:The amount of cartilage chondrocytes rabbits, immobilized with a cast and given oral simvastatin more than the rabbits immobilized with a cast without giving simvastatin. COMP rabbit serum level immobilized with a cast given oral simvastatin lower than rabbits immobilized with a cast without giving simvastatin.