A suitable experimental animal model of osteonecrosis of the femoral head for the evaluation of novel therapeutic trials

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Introduction: Recently there has been novel treatments of osteonecrosis of the femoral head (ONFH), especially for the early stages. The use of biologic substances or their recombinants, such as growth factors have been proposed. However, the major problem in studying novel therapeutic trials of human ONFH is the lack of a suitable experimental model of ONFH. The purpose of this paper is to develop a suitable animal model of ONFH, which allows the evaluation of different therapeutic trials for the pre-collapse stage of ONFH.

Materials and Methods: Twenty five adult male Japanese white rabbits were used. Healthy animals and the animals treated after 4, 8, 12, 24 weeks (n=5) were histopathologically examined. The right hip was experimented on in all treated rabbits. The lateral joint capsule was resected, accompanied by coagulating of the soft-tissue attachments from femoral surgical neck and acetabulum. All the rabbits were injected once with 40 mg/kg of methylprednisolone (MPSL) into the gluteus muscle. The sections were graded according to the histologic stages. Macro photographs and μCT were used to evaluate the femoral head. This study was approved by the ethics Animal Research Committee, Graduate School of Medicine, Kyoto University, Japan.

Results: Macroscopic examination: In the non treated left femoral heads and healthy animals, neither deformities nor loss of the sphericity were detectable. After 8 and 12 weeks flattening were detected. At 24 weeks all the specimen showed degenerative changes. (Fig. 1A-D)

Histological examination: The incidence of ONFH in the treated right hip joint was 20% at 4 weeks, 80% at 8 weeks, 80% at 12 weeks, 60% at 24 weeks. (Table 1) The specimens with ONFH at stage 2 showed the enlargement of the marrow fat cells. At 8 weeks, appositional bone formation and granulation tissue were also detected around the subchondral necrotic tissue. (Fig. 2C,D) At 24 weeks, different stages were detected in same specimen. The non treated left femoral heads did not show ONFH.

Discussion: For the evaluation of novel therapeutic trials of human ONFH, the necessary conditions are the following. (1) a traditional animal for musculoskeletal research, (2) induced by the similar mechanism of human ONFH, (3) close concordance with the pathological features both the early- and late-stage of human ONFH, (4) highly reproducible. The results of our study satisfied these four requirements.

First, rabbits were chosen for this study. Because many articles about osteonecrosis (ON) or ONFH have been reported. Second, the authors first used the methods combining corticosteroids and surgical method. Since steroid-independent ONFH in humans is known to represent half of all patients, we used the high dose of MPSL. ON was induced by corticosteroid administration alone. But their ON was not found in the epiphysis, and the extent was small. To interfere with the blood circulation of extraosseous blood supply, surgical capsule resection was performed. Other methods such as cervical neck fracture and dislocation are not suitable for the evaluation of novel therapeutic trials because their models do not allow normal skeletal healing. ONFH was also induced by the method of chemical toxic agents. However, their model has little in common with human ONFH, and did not simulate the pathological state of human ONFH. Third, our animal model demonstrated that the essential histopathologic features of human ONFH from early to end-stage. In our rabbits the most extensive pathology was located at the superior-lateral aspect similar to human ONFH. Fourth, our model is highly reproducible for the frequent development of ONFH in a simple and reliable way.

Summarizing the findings of reviewed animal models, we could not find a reliable and standardized animal model. In conclusion, the treatment combining the administration of high dose corticosteroids and capsule resection induced highly reproducible ONFH. This rabbit model presents histological characteristic similar to human ONFH. This model would be useful in designing phamaceutics and novel therapeutic trials of ONFH.


Results. Incidence of ONFH and histologic stages.

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<tr>
<th>Stage</th>
<th>4 wks</th>
<th>8 wks</th>
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Stage 1; Dissapearance of the hematopoietic marrow, separation of the lipocytes by edema or hemorrhage, and presence of foam cells. Stage 2; Necrosis of the fatty marrow. Stage 3; Medullary and trabecular necrosis. Stage 4; Complete necrosis with dense medullary fibrosis and formation of new bone in apposition to the dead trabeculae. Ten high-powered fields of each specimen were examined and each was graded, with Grade 0 indicating no empty osteocyte lacunae; Grade 1, fewer than three; Grade 2, three to six; and Grade 3, more than six.

Fig. 1 Macrophographs and μCT images of right femoral heads after the treatment.

Fig. 2 Note the evident collapse with segmental cartilage defect at 8 weeks. Photomicrographs from the same animal develop ONFH with stage 4.