

Animal Experiments Using Rotator Cuff

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In conducting animal studies using rotator cuff, researchers should select the appropriate types of animals and experimental models. This should also be followed by complete understanding of the selected experimental animals as well as the methods for evaluating the results. Thus, researchers could minimize errors and failure in conducting animal experimental studies. Further, this will provide a basis of establishing new idea and theory about rotator cuff diseases.

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Introduction

An animal study is an intermediate one between the laboratory and clinical studies. From the view point that it is conducted prior to clinical studies, it is commonly referred to as pre-clinical study. An animal study is one of the methods for evaluating new theory or treatment modalities on a whole-body scale in a well-controlled, consistent environment. It is probable that clinical studies can be conducted or clinical applications can be rejected based on the results of animal studies. Conversely, animal studies are also conducted to interpret the results of clinical study or to clarify the relevant mechanisms. In conducting animal studies, researchers should determine the study objectives, the type of experimental animals in creating a certain type of animal models and the methods for evaluating the results. In this article, we discuss the actual procedure of animal studies based on the above viewpoints in conducting animal studies using rotator cuff (Fig. 1).

Main Subjects

Study Objectives

The subject matters of studies using animal rotator cuff can be classified into the following:

- (1) Etiology
- (2) Surgical technique
- (3) Rehabilitation
- (4) The effects of prosthesis and reinforcing materials

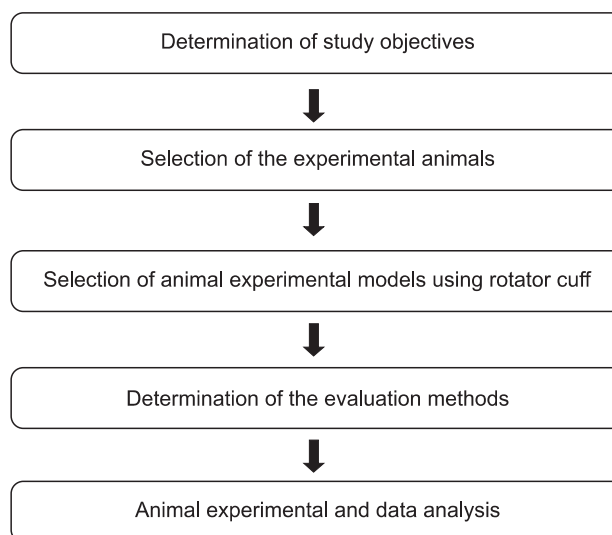


Fig. 1. Flowchart for the process of animal studies using rotator cuff.

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- (5) The effects of cellular or biological additives
- (6) Alternative or adjuvant treatment modalities
- (7) The actions of local and systemic factors

The etiologies of diseases occurring in the rotator cuff may include age-related impingement syndrome,¹⁾ muscle atrophy and fatty degeneration,²⁾ the functions of tendon, cartilaginous changes after the onset of rotator cuff tear, shoulder stiffness, and the effects on the adjacent anatomical structures such as the long head of biceps tendon. In addition, researchers may also consider such matters as the difference depending on the location of rotator cuff tears, the optimal timing of surgery, and postoperative changes in the bone strength. As the surgical technique, researchers may compare between various types of suturing methods,³⁾ the appropriate sites for the insertion of anchor, the adjustment of pressure and tension for sutures, and the preparation methods for the footprint. With regard to the rehabilitation, researchers may consider the effects of exercise and immobilization after operation.⁴⁾ Moreover, subject matters may also include the difference depending on the types of anchor and the effects of various patch grafts on the tendon-to-bone healing.⁵⁾ Furthermore, researchers may also consider the effects of various growth factors,⁶⁾ stem cells⁷⁾ or platelet-rich plasma.⁸⁾ Besides, the effects diabetes,⁹⁾ smoking,¹⁰⁾ hypercholesterolemia,¹¹⁾ parathyroid hormone,¹²⁾ vitamin D,¹³⁾ various types of nonsteroidal anti-inflammatory drugs¹⁴⁾ and steroids,¹⁵⁾ botulinum toxin,¹⁶⁾ local anesthetics,¹⁷⁾ low intensity pulsed ultrasound¹⁸⁾ or extracorporeal shock wave may also be of interest to readers. Once researchers have determined the subject matter of the study, they should consider the anatomical sites that they should evaluate. In conducting studies about rotator cuff, the anatomical sites would be muscle, bone or tendon-to-bone junction.¹⁹⁾ In studies about the muscles, researchers would evaluate changes in the muscle fiber, muscle atrophy or fatty degeneration.⁷⁾ In studies about tendon, researchers would evaluate the maturity of collagen fiber and the characteristics of tenocytes and fibroblasts.²⁰⁾ In studies about the bone, researchers would evaluate changes in the bone mineral density and the degree of the expression of osteoblasts and chondroblasts.²¹⁾ In particular, the tendon-to-bone junction is a region of interest in studies about rotator cuff, for which researchers would evaluate the types, orientation and continuity of collagen fibers, the degree of fibrocartilage and tensile strength.⁸⁾

The Selection of Experimental Animals

In conducting studies about rotator cuff, researchers use such experimental animals as rats,²⁾ rabbits,⁷⁾ dogs,²²⁾ lambs,⁵⁾ goats²³⁾ and monkeys.²⁴⁾

Firstly, rats are characterized by morphological findings that the supraspinatus tendon passes below the arch, which is similar to those of humans.¹⁾ They are the most frequently used to create an animal experimental model because they are cheap

and a large number of animals are available for experimental procedures. In particular, the etiology of various types of rotator cuff diseases has been elucidated in an animal experimental model using rats.²⁵⁾ Due to the presence of various molecular markers, they can be easily used for molecular biological tests.¹⁹⁾ However, their rotator cuff is of small size. This may make it difficult to perform surgery and assessment. Moreover, they exhibit an excellent profile of regeneration. It is therefore probable that it would be difficult to analyze the results of the experiment due to spontaneous recovery after the onset of rotator cuff tear.

Secondly, rabbits are also advantageous in that they are cheap and can be easily bred. In particular, the natural course of fatty degeneration has been clarified in the literature.²⁶⁾ Therefore, they can be easily applied to studies about fatty degeneration. They are also disadvantageous; however, in that the shoulder joint is a weight-bearing one and the supraspinatus tendon and its adjacent structures are different from those of humans.²⁷⁾ This has led to the development of an animal experimental model using the subscapularis tendon below the coracoid process, for which studies have been conducted in a limited scope.²⁷⁾ But there are some problems due to the deep location and severe degree of retraction.

Thirdly, large sized experimental animals, such as dogs, lambs and goats, are also used to create an animal experimental model of rotator cuff tear. In Korea, however, lambs cannot be used for such studies because of breeding problems. As the large sized animals walk on four feet, their mobility is limited as compared with humans in that their shoulder joint is a weight-bearing one and they perform only extension and flexion. Studies using the rotator cuff of large sized animals have been mainly conducted using the infraspinatus tendon.²²⁾ The size of infraspinatus tendon in dogs is as approximately half as humans.²⁸⁾ Mongrel dogs are not too expensive and they can be easily supplied. Therefore, they can be considered as experimental animals for rotator cuff model. The size and shape of the infraspinatus tendon in goats are very similar to those of humans.⁵⁾ Thus, they can be easily used for animal experiments simulating surgical procedures using implant materials in humans. In addition, they also have a similar profile of biomechanical properties.²⁹⁾ This makes them to be an appropriate model for biomechanical studies. But it is difficult to breed them. Typically, goats as well as dogs are disadvantageous in that the anatomical characteristics of their rotator cuff are quite different from those of humans. In particular, their shoulder joint is characterized by a lack of the clavicle, the prematurity of acromion and coracoid process, the discrete presence of infraspinatus tendon as an extraarticular structure outside of the bursa.²⁹⁾ These features are different from humans. In addition, due to a lack of species-specific probes or reagents, it would be difficult to perform molecular biological tests using goats or dogs (Table 1).²⁹⁾

Finally, monkeys can also be used to create an animal experi-

Table 1. Characteristics of Animal Experimental Models of Rotator Cuff

	Rat/mouse	Rabbit	Dog or goat
Advantage	Comparable anatomy to human Widely available Inexpensive Lowest demand Large number is possible	Appropriate for the investigation of fibrofatty infiltration Relatively inexpensive Low demand	Close to human size Use of standard technique Appropriate for the investigation of biomechanical properties
Disadvantage	Small size Significant fatty infiltration in only with nerve transection High healing potential	Weight bearing joint Subscapularis model	Limited movement direction Weight bearing joint Different anatomy from human Infraspinatus model Expensive High demand
Research aim	Tendon-to-bone healing Pathomechanism (age-related degeneration, intrinsic and extrinsic injury) Molecular pathway Rehabilitation Effect of cells and biologic additive Effect of systemic factor	Tendon-to-bone healing Muscular change Effect of cells and biologic additive Effect of scaffold augmentation	Tendon-to-bone healing Mechanical strength Repair technique Effect of scaffold augmentation
Price	10,000 KRW/animal	50,000 KRW/animal	400,000 or 1,000,000 KRW/animal

KRW: Korean won.

mental model for rotator cuff.²⁴⁾ Due to such problems as the complex legal procedure for experiments, high cost, breeding and ethical issue, they are not available for experimental studies about rotator cuff at the moment in Korea.

Selection of Animal Experimental Models Using Rotator Cuff

Depending on surgical sites, animal experimental models using rotator cuff can be a rat model of supraspinatus tendon,²⁰⁾ a rabbit model of subscapularis tendon⁷⁾ and a large-animal model of infraspinatus tendon.⁵⁾ It is a matter of course that a rabbit model of supraspinatus or infraspinatus tendon and large-animal models of supraspinatus tendon using dogs or goats are also available. In this section, however, we'll discuss representative animal experimental models of rotator cuff for each experimental animal.

A rat model of supraspinatus model is a representative one which used the most frequently to examine rotator cuff using experimental animals. As described above, there is a similarity in the adjacent environment to the supraspinatus tendon between rats and humans.¹⁾ Therefore, etiologies of diseases that occur in the rotator cuff have been well investigated in a rat model. Using the rat model, nearly all types of researches are possible including the elucidation of the relevant molecular biological mechanism to various rotator cuff diseases.

Rabbit models of subscapularis tendon are created based on the similarity in the anatomical characteristics between the subscapularis tendon complex constrained by subcoracoid bony tunnel and the coracobrachialis muscle in rabbits and

the supraspinatus tendon complex constrained by subacromial bony tunnel and the coracoacromial ligament in humans.²⁷⁾ In addition, the shape of the lesser tubercle where the subscapularis tendon is inserted in rabbits shows similar characteristics to that of the greater tubercle where the supraspinatus tendon is inserted in humans.²⁹⁾ The size of the lesser tubercle in rabbits is approximately 1/4 of the greater tubercle in humans.²⁹⁾ To date, however, only a small number of studies have been conducted probably due to the complexity of the surgical procedures coming from a small tendinous portion of the rabbit subscapularis, a significant retraction of the torn subscapularis, and a difficulty in exposure.

Nearly all the studies about rotator cuff in dogs and goats have been conducted using the infraspinatus tendon.²³⁾ An access can be easily made for experimental animals placed in a lateral decubitus position. Particularly in goats, the size and biomechanical properties of the infraspinatus tendon are very close to those of humans.²⁹⁾ Therefore, they are frequently used to create an experimental model for the purposes of evaluating the biomechanical effects of implants or augmenting materials as well as surgical technique. But the infraspinatus tendon is an extraarticular structure that is present outside of the bursa and its anatomical structure is different from that of human.²⁹⁾ This limits the interpretability of the results of biological repair. In addition, there are no molecular markers for molecular biological studies.²⁹⁾ Most of the dogs and goats are used to assess the results of biomechanical studies.

Most of rotator cuff diseases are chronic ones accompanied by the degenerative changes. It can therefore be inferred that an

animal experimental model of rotator cuff, reflecting the chronic diseases, would be more useful to simulate the clinical setting. After substantial periods of time after the resection of the rotator cuff, chronic animal models can be created. We also have experiences about creating a chronic animal model by leaving the torn tendon for six weeks and enclosing that with the use of penrose drain for the prevention of the adhesion to the adjacent tissue following the dissection of the subscapularis and supraspinatus tendon in rabbits.⁸⁾

In addition, an impingement model has been established to induce the intrinsic or extrinsic impingement.²⁵⁾ To induce the intrinsic impingement, inflammatory responses are triggered using injections of collagenase.¹⁾ To induce the extrinsic impingement, animal experimental models have been created in such a manner that the Achilles tendon is placed under the acromion¹⁾ or bone graft is performed.³⁰⁾

Other animal models of rotator cuff may include an overuse model where experimental animals are induced to run on a treadmill for the purposes of triggering the occurrence of repeated microtears and degenerative changes,³¹⁾ an immobilization model where the plaster cast is applied to the shoulder joint³²⁾ and a denervation model where the fatty degeneration of the rotator cuff is induced through the dissection of the suprascapular nerve.³³⁾

But if there is a lack of the established animal experimental models that are appropriate for the subject matters, researchers would create a new model. It can be stated that it would provide a basis of various types of further researches if there are any chances that researchers create a new animal experimental model. This would be of great significance.

As described here, after selecting experimental animals and the relevant models based on their subject matters, researchers would perform surgical operations or other procedures. Then, they would perform experimental procedures to evaluate the results after certain periods of time.

Methods for Evaluating the Results

Methods for evaluating the results of animal studies may include gross appearance, biomechanical evaluation, histological evaluation, immunohistochemical evaluation and radiological evaluation. In particular, biomechanical and histological tests are essential for assessing the results of animal experimental studies.

On gross examination, researchers evaluate the detachment of rotator cuff from the bone, the degree muscle atrophy, the color or the weight of muscles, and the thickness and width of rotator cuff tendon.^{7,26)} Moreover, researchers may also measure the contact pressure and area by placing the pressure film between the rotator cuff tendon and the bone and performing various types of suturing.³⁴⁾

A biomechanical test is a tensile testing where researchers assess the solidity of tendon-to-bone healing with the traction of

rotator cuff tendon inserted in the bone. In the biomechanical test, researchers are required to use instruments for fixing the humerus and tendon and pulling the tendon from the bone. Instruments for fixing the humerus and tendon are commonly designed by researchers. According to a review of literatures, various types of these instruments have been designed and then used for animal experimental studies.^{35,36)} As the factors that are measured on biomechanical test, there are mode of failure and various parameters derived from the stress-strain curve or load relaxation curve. The mode of failure means the specific sites where the failure occurred, which may include the avulsion of the humerus, the insertion sites, the parenchyma of the tendon and the fixation sites of clamp.³⁷⁾ As a whole, the rupture at the parenchyma of the tendon is referred to as stronger tendon-to-bone healing.⁸⁾ Various parameters on both the stress-strain curve and load relaxation curve may also be used. It can be stated, however, that load to failure is the most important indicator of the strength of tendon-to-bone healing.⁷⁾ In addition, it would be mandatory to measure the load to failure, which is essential for performing the biomechanical test.

A histopathologic examination is a laboratory process where various types of staining methods are performed. It is commonly encountered that the tissue sectioning, fixation, paraffin-embedding, staining and slide preparation are performed with the help of the department of pathology or reference laboratories. Thus, the selection of the specific staining method rather than the tissue preparation would be more important. Staining methods for animal experimental studies about rotator cuff include hematoxylin and eosin staining for examination of the overall morphology and density of the cells,³⁸⁾ Oil Red O and osmium tetroxide staining for examination of the adipose tissue in the muscles,³⁹⁾ Masson's trichrome staining and Picrosirius red for examination of the connective tissue and collagen fibers,⁴⁰⁾ Safranin O staining and Toluidine blue staining for examination of cartilages based on proteoglycan-positive staining properties¹⁶⁾ and Verhoeff-van Gieson staining for examination of elastic fiber. These staining methods are used to examine the muscles, tendons, bone and cartilage, tendon-to-bone insertion site, and graft materials. Basically, the cellularity, vascularity and inflammation rates are checked. In addition, the muscle fibers, connective tissue and adipose tissue in the muscle, and the organization and maturation of the collagen fibers as well as fibroblasts and tenocytes in the tendon are examined using the above staining methods for the muscle and tendon. At the junction between the tendon and the bone, staining methods are used to assess the orientation and the continuity of the collagen fibers between tendon and bone, the fibrocartilage, and the degree of the granulation tissue formation. Moreover, the staining methods for the cartilage are used to assess the surface irregularity, the degree of staining property and that of the maintenance of tidemark. In addition, the formation of new bone, the organization of and

the connectivity to graft materials and the degree of the absorption of graft materials can be assessed. The arrangement of collagen fibers can be accurately on confocal microscopy and polarized light microscopy although it can also be examined using conventional types of light microscopy.⁴¹⁾ Both semi-quantitative and quantitative methods can be used for the evaluation. As a whole, however, semi-quantitative methods are used. It is also probable that such imaging software as the Image J software or Photoshop software may be used for quantitative analyses.⁴¹⁾ In general, the cellularity is measured as the number of cells per unit area and the shape of the cells is given 1 point as it becomes close to the round shape (0 to 1 point).³⁸⁾ In the assessment of the muscle tissue, the size of muscle fibers is measured based on the distribution of actual measurements of their width and area.⁴²⁾ In addition, the degree of the muscle atrophy and the deposition of adipose cells are evaluated using semi-quantitative methods based on a 4- (no/a few/some/many) or 5-point scale (no/minimal/mild/moderate/severe).⁷⁾ Furthermore, semi-quantitative methods can also be considered to evaluate the tendon-to-bone junction based on the relevant grading system.⁸⁾ This may also be accompanied by the use of conventional scoring system such as the Movin score and Bonar score⁴³⁾ or tendon maturation score.⁴⁴⁾

Immunohistochemical and fluorescent staining methods are used to confirm the presence of specific materials that are present in the tissues or cells with the use of antigen-antibody reaction.²⁰⁾ That is, they are based on the methods for detecting antigens by labeling antibodies with a specific type of materials. Representative markers include fluorescent dye or enzymes such as peroxidase. Examinations are routinely done using light microscopy or epifluorescence microscopy. To date, various types of markers have been established in rats and rabbits.⁴²⁾ The results are evaluated based on the degree of the expression of target proteins. The accurate sites of the expression of target proteins in the tissues can be identified compared with the Western blotting or polymerase chain reaction (PCR). Immunohistochemical and fluorescent staining methods as well as Western blotting or PCR are also advantages that the molecular pathways can be clarified.⁴⁵⁾

Radiological methods include micro-computed tomography,⁴⁶⁾ magnetic resonance imaging⁴⁷⁾ and ultrasonography,⁴⁸⁾ by which researchers can evaluate the degree of fatty degeneration, muscle atrophy, tendon-to-bone healing, and alterations in the thickness of cartilage.⁴⁶⁻⁴⁸⁾

In addition to these, there are also methods based on electrophysiology, such as electromyography, where active electrodes are placed in the target muscle and reference electrodes are placed in the tendons that are adjacent to the sites of bone insertion.⁴⁹⁾ Then, the electrical activity of the target muscle is evaluated with the stimulation of nerves innervating the target muscle at the supramaximal intensity.⁴⁹⁾ These methods are character-

ized by the functional assessment rather than the morphological one.

The assessment can be done at the single time point, but it may also be done at more than two time points. It would be desirable; however, to perform the assessment at more than two time points, which is essential for analyzing time-dependent changes. According to a review of literatures, assessments have been performed until 16 weeks in rats or rabbits and 26 weeks in dogs, lambs or goats.^{50,51)}

Conclusion

In conducting animal studies using rotator cuff, researchers should select the appropriate types of animals and experimental models. This should also be followed by complete understanding of the selected experimental animals as well as the methods for evaluating the results. Thus, researchers could minimize errors and failure in conducting animal experimental studies. Further, this will provide a basis of establishing new idea and theory about rotator cuff diseases.

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