LOCAL ADMINISTRATION OF OSTEOGENIC PROTEIN-1 INHIBITS REDUCTION OF STRUCTURAL PROPERTIES OF THE OVERSTRETCHED ANTERIOR CRUCIATE LIGAMENT WITH PARTIAL MIDSUBSTANCE LACERATION

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INTRODUCTION

Overstretched anterior cruciate ligament (ACL) injury with partial midsubstance laceration frequently occurs in various athletic accidents. We have had no therapeutic options to repair this type of ACL injury because the ACL has poor healing potential. The authors have established a useful model of overstretched ACL injury with partial midsubstance laceration [1]. In this model, the maximum load and the stiffness of the ACL significantly decrease to 30% or less immediately after surgery, and then gradually increased to approximately 50% at 12 weeks [1]. Recently, we have reported that a local application of TGF-beta1 significantly inhibits the reduction of structural properties of the partially injured ACL at 12 weeks [2]. However, it has been well known that the intra-articular application of TGF-beta1 induces osteoarthritic changes in the knee joint [3]. Therefore, we should study whether there are any growth factors except for TGF-beta1 that can enhance healing of the ACL injury. Osteogenic protein-1 (OP-1), a member of the TGF-beta superfamily, has been applied to enhance cartilage regeneration [4]. Recently, Alicia et al. [5] reported that OP-1 significantly enhances cell proliferation in a cultured ligament. Therefore, there is a strong possibility that a local application of OP-1 can enhance healing of the injured ACL. No studies, however, have been conducted to clarify the effect of OP-1 application on healing of the injured ACL. We hypothesized that local administration of OP-1 significantly inhibits the reduction of the structural properties of the overstretched ACL with partial midsubstance laceration at 12 weeks. The purpose of this experimental study is to test this hypothesis.

MATERIALS AND METHODS

A total of 21 skeletally mature female rabbits weighing 3.7±0.3 (Mean±SD) kg were used in this study. In each animal, the right ACL was injured using the following quantitative technique [1] (Fig.1). The anteromedial and posterolateral bundles of the ACL were transected at two different levels, the proximal one-third and the distal one-third levels of the ACL, respectively. The ACL was then stretched by applying an anterior drawer force to the tibia at 90 degrees of knee flexion. Subsequently, the ACL length was irreversibly elongated to 110% of the original length. Then, the rabbits were randomly divided into 3 groups of 7 animals each. In Group I, 12.5-microgram OP-1 (R&D Systems) was applied with 0.2-ml phosphate-buffered saline (PBS) around the injured ACL. In Group II, 0.2-ml PBS was applied as the sham treatment around the injured ACL. In Group III, no treatments were applied to the knee to obtain the control data on the natural course of the injury. In each animal, no immobilization was applied after surgery. The animals were allowed unrestricted activities in their cages. All animals were sacrificed at 12 weeks after surgery. Seven ACLs randomly harvested from all the left knees (Group N) were used to obtain normal control data. In each group, 5 of the 7 rabbits were used for biomechanical evaluation, and the remaining 2 were used for histological observation. In biomechanical evaluation, the anterior-posterior (A-P) translation of the tibia to the femur was measured using a tensile tester with a 3-DOF fixture under +/-10N forces at 30, 60, and 90 degrees of knee flexion. The cross-sectional area was then measured with a non-contact optical method using a video dimension analyzer [6]. The structural properties of the femur-ACL-tibia (FAT) complex were determined in tensile testing at a cross-head speed of 20 mm/min. Statistical analyses were made using the ANOVA with the Fisher’s post-hoc multiple comparisons.

RESULTS

Concerning the A-P translation of the tibia to the femur or the cross-sectional area of the ACL, there were no significant differences in the 3 groups (Fig.2). Regarding failure modes, all specimens failed at the midsubstance in Groups II, and III, while the ACL insertion was avulsed in 3 and 5 specimens in Groups I and N, respectively. The ANOVA demonstrated a significant difference in the stiffness (p<0.0001) and the maximum load (p<0.0001) among the 4 groups (Fig. 3-A, B). The post-hoc test showed that the stiffness and the maximum load of Group I were significantly greater than those of Groups II (p=0.0109 and p=0.0117, respectively), while they were significantly less than those of Groups N (p=0.0285 and p=0.0002, respectively). There were no significant differences between the Groups II and III in these parameters. Histologically, alignment of collagen fibers appeared to be irregular in the midsubstance of the ACL with numerous cells having a small round nucleus in the treated groups. Any abnormal findings were not observed in the joint cartilage.

DISCUSSION

This study clearly demonstrated that intra-articular administration of 12.5-microgram OP-1 significantly inhibited the reduction of the structural properties of the overstretched ACL with partial midsubstance laceration at 12 weeks. This is the first report that a local application of OP-1 significantly affected healing of the ACL. Because it is known that the OP-1 is not harmful for the joint cartilage, this study implied that OP-1 might be able to be used for a therapeutic application to enhance healing of the injured ACL in the future. However, this study showed that the OP-1 administration cannot significantly affect the A-P translation of the knee. This result suggested that the OP-1 administration cannot reduce the length of the overstretched ACL.

REFERENCES


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