Influence of the Mechanical Environment upon the Healing of Segmental Bone Defects in a Rat Model Studied with a Novel External fixator

[1]V. Glatt, [2]R. Matthys, [1]A.Ivkovic, [1]C. Evans

[1]*Department of Orthopaedic Surgery, Harvard Medical School, Boston, MA, US,*

[2]*AO Development Institute, Davos, Switzerland*

INTRODUCTION: Despite the intrinsic ability of bone to heal, there are still numerous clinical circumstances where bone healing is defective and demands the attention of the physician. Common examples include the delayed and non-union of fractures, and the loss of large segments of bone after traumatic injury, tumor resection and failed arthroplasty. There are several surgical approaches to enhance the healing of human bones, and these have been supplemented in recent years by the introduction of recombinant, human bone morphogenetic proteins -2 and -7 (BMP-2 and BMP-7) into clinical practice in combination with different fixation devices. Over the years there have been many advances in technology, which helped to improve the fixation for critical sized defects. Despite these improvements, the clinical management of critical-sized defects remains problematic for surgeons today because it isn't clear how stiff or flexible the fixation device should be to optimize bone healing. Our project is based on the hypothesis that the healing of critical-sized defects in response to BMP-2 can be dramatically improved by manipulating the mechanical environment within the defect. Accordingly, this project aims to investigate the influence of the mechanical environment on bone healing in response to BMP-2 in a rat, critical-sized defect model. The mechanical environment of the defect is altered with a custom made external fixator whose stiffness can be changed in a reliable, quantitative fashion.

METHODS: Novel, second generation, external fixators that can be adjusted to provide three different stiffnesses were designed specifically for the rat femur. All materials in the fixator were chosen to be the same as used clinically for human implants. The screws for a new external fixator are made out of titanium (Ti). The stability bars are made out of polyetheretherketones (PEEK). The diameter of the screws is 1mm and the length is 12.75mm. The distance between the screws is 4mm and the distance between the middle screws is 11mm. All holes are predrilled using a 0.79mm drill bit. The screws are locked in the corresponding holes of the fixator, which is parallel to bone surface and set at the distance of 5mm. The fixator stiffness can be changed by changing the stability bars to provide stiffnesses of 40, 70 or 100%, as required. To create reproducible 5mm defects in all rats the guide was designed for a giggly saw that clips on the external fixator in between the two middle screws. A rat, femoral, critical-sized defect model was used to test this fixator in-vivo. A 5mm defect was created in 6 Sprague-Dawley rats and treated with rhBMP-2 applied on a collagen sponge with external fixators providing 40, 70, 100% stiffness. Animals were x-rayed weekly for 8 weeks to monitor bone healing.

RESULTS: A second generation external fixator prototype was successfully created and manufactured for testing in-vivo (Figure 1). An in-vivo pilot study showed that the there is a difference in bone healing depending on external fixator stiffness. Weekly x-rays revealed that bone callus size was biggest in the group with the lowest stiffness (40%) fixator. Furthermore, early callus formation was seen in this group and 70% stiffness group after 9 days of treatment. However, the group with 100% stiffness external fixator had no callus formation after 9 days of treatment. In this group callus formation was delayed until after two weeks of treatment. By the third week defects were bridged with all fixation methods with the biggest callus in 40 and 70% stiffness fixators and smaller callus with 100% stiffness (Figure 2).

Figure 1 External Fixator with saw guide

DISCUSSION & CONCLUSIONS: Loss of large segments of bone leads to critical-sized defects that fail to heal spontaneously. Although healing can be induced by recombinant, human bone morphogenetic protein-2 (rhBMP-2), the clinical response is modest. The current project focuses on the influence of the mechanical environment on the healing of critical sized segmental defects in response to rhBMP-2. In preliminary studies, using a first generation external fixator to stabilize the defect, we have been able to achieve osseous union using rhBMP2 and BMP-2 gene transfer with an adenovirus vector. However the rate of healing and the mechanical properties of the healed bone are inconsistent. We hypothesized that this is due to insufficiencies in the rigid external fixator, which generates an unfavorable local mechanical environment. Therefore, we have designed a new, second generation external fixator which allows us to control and measure with precision, the mechanical environment within the critical-sized segmental defect in-vivo. Our pilot study shows that fixator stiffness is important in the biologic process of healing bone. In fact, from the weekly x-rays we observed that with 40 and 70% stiffness fixator callus formation was seen already after 9 days of treatment, whereas defects subjected to 100% stiffness had no callus. Furthermore, after two weeks bone regeneration was seen in all groups, but two lower stiffness groups had bigger callus formation as compared to the stiffest fixator. This confirms findings in the literature that if there is too much micro motion during healing, bone bigger callus forms (1) Material, structural and mechanical testing will be performed to determine how important early callus formation and size is to the physical properties of the healed bone. We will apply this knowledge to manipulate fixator stiffness through the course of healing to get rapid bone regeneration and best quality of healed bone. The findings from this study will be highly relevant to the surgical management of patients with segmental bone defects and, possibly, delayed and non-union fractures.

REFERENCES: 1. Gomez-Benito MJ, Garcia-Aznar JM, Kuiper JH, Doblare M 2006 A 3D computational simulation of fracture callus formation: influence of the stiffness of the external fixator. J Biomech Eng 128(3):290-9.

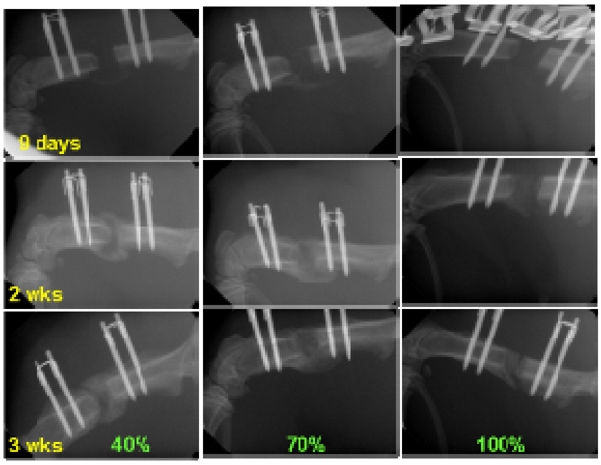

Figure 1 Representative x-ray images with 40, 70 and 100% stiffness external fixator after 9 days, 2 and 3 weeks of treatment with rhBMP-2.