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Continuous local infusion of fibroblast growth factor-2 enhances consolidation of the bone segment lengthened by distraction osteogenesis in rabbit experiment

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Abstract

Experimental tibial lengthening was achieved in 61 rabbits to examine the effect of continuous local infusion of recombinant human fibroblast growth factor-2 (rhFGF-2) on bone healing of the lengthened segment. The tibial diaphysis was separated by osteotomy and was subjected to slow progressive distraction (rate: 0.35 mm/12 h) using a monolateral external fixator. There were a lag phase for 1 week, a distraction phase for 2 weeks, and a consolidation phase for 5 weeks in this experiment. At various stages of distraction, rhFGF-2 was infused continuously for 2 weeks into the lengthened segment (rate: 14.28 μg/60 μl/day) using an osmotic pump implanted under the skin. Bone healing was significantly accelerated when rhFGF-2 was infused in the beginning of consolidation phase, but not in the distraction phase or in the lag phase. Infusion of normal saline (N/S) using the same osmotic pump had no effect. Dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computerized tomography (pQCT) studies demonstrated that rhFGF-2-treated tibia had increased bone mineral density (BMD), bone mineral content (BMC) and cortical bone thickness (CBT) when compared with N/S-treated tibia. Three-point bending test demonstrated that rhFGF-2-treated bone had significantly stronger mechanical properties than N/S-treated bone. Finally, distribution of the infused materials was checked by using Indian ink or radio-opaque. The dyes distributed widely but exclusively in the lengthened segment. Based on these results, we conclude that direct delivery of rhFGF-2 into the lengthened segment can shorten the consolidation phase of limb lengthening and the method is applicable to the clinical treatment.

Keywords: Local injection; FGF-2; Distraction osteogenesis; Osmotic pump; Limb lengthening

Introduction

Recent advances of external fixation and newer knowledge of distraction osteogenesis have brought a revolution in surgical treatment of congenital or post-traumatic short extremities. Various types of external fixation devices have been developed to achieve limb lengthening and simultaneous correction of the complex bone deformities [1–3]. Lengthening a bone for more than 10 cm is now possible, if the proper technique is used. Principle of distraction osteogenesis has also been applied in treatment of segmental bone loss, infected nonunion and congenital pseudoarthrosis of the bone [4,5].

We have been engaged in studying the basic mechanism of distraction osteogenesis using animal models of limb lengthening [6–10]. Biological events of distraction osteogenesis are understandable if the treatment process is divided into three distinct phases, i.e., a lag phase, a distraction phase, and a consolidation phase. During the lag phase after osteotomy, blood circulation recovers and immature callus is formed around osteotomy site [8]. During distraction phase, new bone regenerate is continuously formed within the lengthened segment. During consolidation phase, the lengthened segment matures and bone union is obtained while the external fixator is still on.

The factors affecting bone healing during distraction osteogenesis may include type of osteotomy, timing and rate of distraction, stability of fixation, age of the patient and underlying disease. Although the efforts to improve osteotomy techniques and stability of fixation [8,11,12], the overall treatment time of limb lengthening still requires a long period. Healing indices, calculated by dividing the treatment time with the amount of lengthening, ranged from 28 to 36 days/cm

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[8,13–15]. The patient has to tolerate wearing a bulky external fixator at least for several months until consolidation of the lengthened segment is obtained.

Several authors have attempted to promote bone formation during distraction osteogenesis by local administration of growth factors or cytokines [16–19]. Okazaki et al. [16] reported that a single-shot injection of rhFGF-2 into the regenerating bone was effective to stimulate bone healing in rabbit tibial lengthening. In the present study, we are demonstrating that continuous local infusion of a low-dose rhFGF-2 into the lengthened segment can accelerate bone healing of the lengthened segment in rabbit model.

Materials and methods

Animals

Animal experiment was carried out on 61 male Japanese white rabbits, weighing 1.8 to 2.2 kg, purchased from Oriental Yeast Co. (Tokyo, Japan).

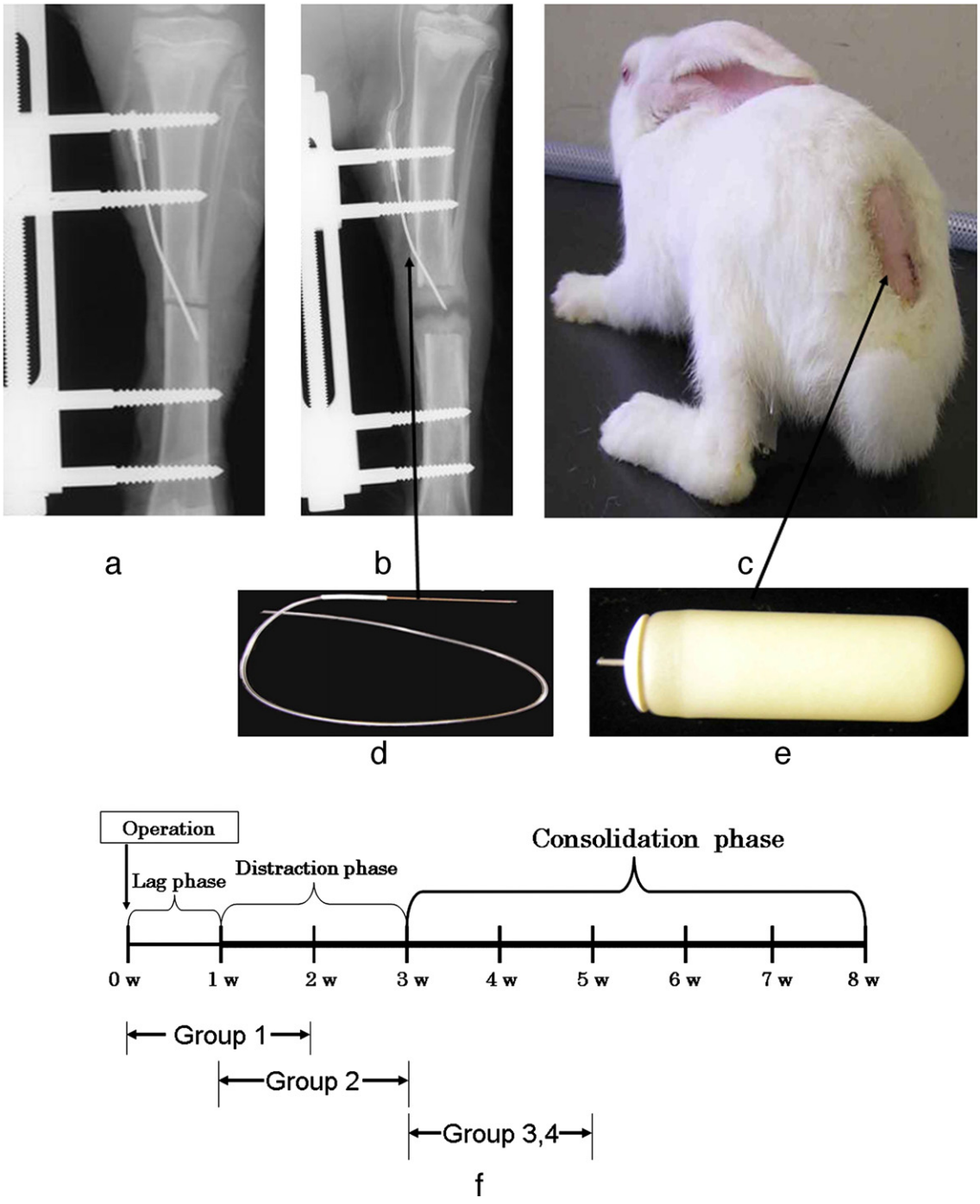

Fig. 1. Experimental design: Radiographs showing the position of the needle at the time of operation (a) and at the end of distraction (b). The osmotic pump (e) was implanted subcutaneously on the back of a young rabbit (c). The pump was connected to a plastic catheter (d) that reached the needle (a, b) inserted into the lengthened segment. Local infusion of rhFGF-2 was achieved for 2 weeks at various stages of the experiment (f). The animals were sacrificed 8 weeks after operation.