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The missing effect of human recombinant Bone Morphogenetic Proteins BMP-2 and BMP-7 in surgical treatment of aseptic forearm nonunion

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ABSTRACT

Introduction: In this cohort study, the surgical revision concept of open compression plating and autologous bone grafting with and without additional application of BMP for treatment of aseptic ulna and/or radius shaft nonunion was evaluated. The purpose was to evaluate the clinical and radiological outcome, and to determine any difference in osseous healing, range of time between revision surgery and bone healing, and postoperative complications between the cohort groups.

Patients and methods: Between 01/2005 and 03/2015, a prospective, randomised, controlled cohort study was performed in a Level I Trauma Centre. Forty-nine patients were treated with the diagnosis of aseptic diaphyseal ulnar and/or radial shaft nonunion using compression plating and autologous bone grafting. Additional biological augmentation using BMP-2 or BMP-7 was performed in 24 patients. Clinical and radiological follow-up was performed six weeks, three and six months after revision surgery in accordance to the system by Anderson.

Results: The study group consisted of 38 men and 11 women with a median age of 44 years (range 19–77). Twenty-four out of 49 patients obtained compression plating either with autologous iliac crest bone grafting (11/24 patients) or cancellous bone grafting (13/24 patients) and additional application of BMP-2 (4/24 patients) or BMP-7 (20/24 patients). The remaining 25 patients did not receive any additional application of BMP, but autologous bone grafting. The median follow-up was 15 months (range 6–54 months). Forty-six out of 49 nonunion healed within 12 months after revision surgery with a median time to union of six months. The clinical outcome, as assessed using the system by Anderson, as well as osseous healing, duration of time interval between revision surgery and bone healing, and postoperative complications did not demonstrate significant differences between the cohort groups.

Discussion: Atrophic/oligotrophic forearm nonunion healed irrespective of additional application of BMP combined with autologous bone grafting. For successful treatment, radical resection of fibrous nonunion tissue and internal compression plate fixation is required with the aim of achieving high degree of rigid stability. Also, correction of angular deformities, restoration of length, and precise axial alignment of the distal radio-ulnar joint are mandatory prerequisites to successfully achieve bone healing.

Introduction

The gold standard for the treatment of radius and ulna shaft fractures in adults is open reduction and internal compression plate fixation. This technique is well established and has shown low complication rates such as malunion, nonunion, and loss of function [1]. Risk for delayed fracture healing or development of forearm nonunion is linked to reduced load of undifferentiated mesenchymal cells, less rapid cellular differentiation, thinner periosteum, and reduced osseous vascularisation [2]. Nonunion of forearm fractures remains a challenging problem due to the anatomical structure and function of the forearm. In large cohort studies, the incidence of forearm nonunion or delayed union is reported to reach up to 10% [3–5]. Despite progress in surgical

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techniques and modern implants, operative treatment of diaphyseal aseptic nonunion represents a therapeutic challenge. Anatomical restoration of length, alignment, rotation, restoration of the radio-ulnar articulation, and radial bow are essential for enabling the optimal stabilising effects of forearm muscles and interosseous membrane, range of motion, particularly pronation-supination, and overall function [6]. Recent studies demonstrated that treatment of diaphyseal forearm nonunion using classic techniques of compression plate osteosynthesis and autologous bone grafting resulted in high clinical and radiological union rates. However, a substantial subset of patients had a suboptimal functional outcome [7].

The additional use of autogenous bone grafts was historically described as a successful option for the reconstruction of traumatic segmental bone defects [8]. Biological augmentation with autogenous bone grafting is important in treating the majority of forearm nonunion [9]. The options for bone grafting include non-vascularised structural (cortico-cancellous) [6], and non- structural (cancellous) grafts [10], as well as vascularised grafts. Good to excellent outcomes have been demonstrated [11] despite reports of donor site morbidity related to iliac crest wounds, infection risk, and slow or delayed graft incorporation [12]. No robust data is found regarding the use of human recombinant Bone Morphogenetic Proteins (BMPs) in the upper extremity yet. Only a few case reports describe an inflammatory reaction following the application of BMPs for the treatment of forearm nonunion [13–15].

In this cohort study we evaluated our therapeutic concept for the treatment of aseptic forearm shaft nonunion including open revision, compression plating, and biological augmentation with autogenous bone grafting, with and without additional application of BMPs [16]. The aim of the study was to evaluate this concept in a large number of patients, and to determine if osseous healing of aseptic ulna and/or radius shaft nonunion in a high percentage was depending on additional application of BMPs. Therefore, we evaluated the clinical and radiological outcome, and determined if there was a difference in osseous healing, range of time between revision surgery and bone healing, and postoperative complications between the cohort groups.

Materials and methods

Between 01/2005 and 03/2015, a prospective, randomised, controlled cohort study was performed in a Level I Trauma Centre. The study included forty-nine patients, who were treated for a forearm (ulnar and/or radial shaft) fracture and had developed aseptic diaphyseal ulnar and/or radial shaft nonunion. Fractures were classified according to the AO/OTA classification. Fractures of the proximal fifth of the ulna and radius were primarily excluded from the study. Nonunion was defined clinically and radiologically as absence of healing at least six months after the index operation (Fig. 1a and b), or evident failure of treatment prior to that [10]. Patients with congenital forms of nonunion or skeletal immaturity were excluded. Clinical signs of nonunion included persistent pain, loss of function, forearm deformity, or hardware loosening. Radiological nonunion formation was determined as lack of radiographic bridging of at least three out of four cortices assessed on antero-posterior (AP) and lateral conventional radiologic views. In cases of doubt, a computed-tomography scan was performed to detect radiological nonunion. Patients with previous or consecutive positive bacterial cultures were excluded from the study to restrict the study group to aseptic forearm shaft nonunion. Additional biological augmentation with an autologous bone graft using human recombinant Bone Morphogenetic Proteins BMP-2 (InductOs®; Medtronic Biopharma, Heerlen, The Netherlands) or BMP-7 (OP-1®; Stryker Biotech, Hopkinton, Massachusetts, U.S.A.) was performed in 24 patients [9,17]. Four patients of each cohort group obtained adjuvant therapy including high energy extracorporal shock wave therapy (ESWT) to stimulate bone healing.

Fig. 1. (a) Twenty-three-year-old male patient involved in a motor vehicle accident: development of atrophic ulnar shaft nonunion six months following plate osteosynthesis using a one-third tubular plate of an ulnar shaft fracture at an outside institution. (b) Seventy-seven-year-old male following blunt impact by a bull: atrophic ulnar shaft nonunion six months following plate osteosynthesis using a one-third tubular plate of a forearm shaft fracture at an outside institution. The radial shaft fracture has healed.

Surgical procedure

In general, the previous surgical approach, utilised for primary fracture treatment, is utilised and extended if needed including exploration of the nonunion site. Implant has to be removed and devitalised tissue consequently debrided. Biological environment is ameliorated as indicated by visible bleeding at the nonunion site prior to re-osteosynthesis with additional biological augmentation including application of autologous bone graft, and optional additional application of BMP. Similar to reconstruction of a joint alignment, exact restoration of ulnar and radial length as well as torsion has to be performed. Two holes, one distal and one proximal to the nonunion site, are drilled and screws are inserted. Optionally, an intermediate short plate can be applied. Following internal fixation using this plate, radiological controls of the plate positioning is performed. Consecutively, the iliac crest bone block graft is placed into the nonunion site. BMP was applied to the nonunion area according to manufacturer's instructions as a suspension. To ensure that BMP remains at the nonunion site, the injected suspension was sealed by a periosteal flap in all patients. Finally, a definite compression plate osteosynthesis is performed.

Follow-up

Clinical and radiological follow-up studies were performed at regular intervals, two weeks (Fig. 2a and b), six weeks (Fig. 3a