Case Report
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Treatment of Femoral Non-Union with the Gene-Activated Osteoplastic Material: A Case Report

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Abstract

Background. Non-unions of distal femur fractures are difficult to treat and occur in about 6% of cases. Multifactorial causes of fractures non-unions require individual treatment for each patient in accordance with the “diamond” concept. The standard protocol for patients with atrophic non-unions treatment involves bone autografts using, but there are limitations of size, shape, quality and quantity of autografts. Osteoplastic materials with osteoinductive (angiogenic) and osteoconductive activity can be used as bioresorbable implants in combination with autogenous spongy bone in the treatment of extremities long bones non-unions. ***Clinical case description.*** A 63-year-old patient was admitted to the clinic for non-union of distal third of the femur with bone defect, fragments were fixed with a plate. The examination revealed plate fracture, screws migration (group III according to the Non-Union Scoring System). The volume of supposed bone defect was about 8.5 cm^3. The surgery was performed: plate removal, debridement of the non-union zone, femur defect replacement with a bone autograft in combination with the gene-activated osteoplastic material “Histograft” in a ratio of 1:1, osteosynthesis of the femur with two plates. After 6 months. during the control computed tomography, consolidation was determined (4 points on the REBORNE scale). Pain was practically absent (NRS-2). The range of motion in the knee joint: flexion — 80°, extension — 180°. According to the Knee Society Score (KSS) — 68 points. ***Conclusion.*** In this case report the complete fracture fusion was achieved in patient within 6 months — 4 points on the REBORNE scale. No adverse events were observed. It confirms the safety and efficacy of described method and allows to continue the clinical trials.

Keywords: bone grafting, non-union, bone autograft, osteoplastic material, bone defect.

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Introduction

Distal femoral fractures occur in patients of any age, and account for 3-6% of femoral fractures in adults and 0.4% of all fractures [1]. Non-unions of distal femoral fractures are relatively rare, about 6% [2] and difficult to treat [3, 4]. They may occur after surgery and conservative treatment [2, 3, 4].

The main causes of the distal femur non-unions are inadequate fixation of the fragments, which does not give proper stability, impaired blood supply to the fracture zone due to soft tissue injury, infection, concomitant pathology, as well as the experience of the surgeon [2, 5, 6].

Multifactorial causes of fractures non-unions require selection of individual treatment for each patient, which may include use of tools that form the so-called "diamond concept": osteoconductive matrices, vascularization, growth factors, osteogenic cells and mechanical stability [7], each one should be analyzed and taken into account during treatment. Based on this concept, the priority in atrophic and oligotrophic non-unions treatment according to the classification of Weber and Cech (1976) [8] is angiogenesis stimulation in the non-union zone and repeated mechanical stable osteosynthesis [9, 10, 11].

The generally accepted standard protocol for the atrophic non-unions treatment involves using of bone autografts, but their preparation is associated with risk of complications (0,8–15%) [12, 13], such as inflammation, hematoma formation and chronic pain in the donor area [14, 15]. In addition, the quality of bone autografts may vary among patients depending on gender and age, which limits its clinical use [16]. In addition, there are limitations of size, shape and quantity of autografts [17].

Osteoplastic materials with osteoinductive (angiogenic) and osteoconductive activity are in great demand in clinical practice and can be used as bioresorbable implants in combination with autogenous spongy bone to reduce the need for the latter [18] and prevent of bone regenerate volume loss. This technique is promising for non-unions and long bones defects treatment.

Based on the above, the aim of the study was to evaluate the effectiveness of the gene-activated material based on octacalcium phosphate use, which has angiogenic activity due to its constituent plasmid DNA molecules carrying the vascular endothelial growth factor-A165 (VEGFA) gene, in patients with atrophic and oligotrophic non-unions of the extremities long bones treatment. The protocol of the clinical trial was registered in the international registry clinicaltrials.gov (NCT04705857). The subject of this article is the treatment results of the first group of patients included in the study (the study meets the requirements of the Helsinki Declaration of Revision 2013).

Clinical case

Patient 63 years old, without gross concomitant pathology, was admitted to the clinic for non-union with a bone defect of the lower third of shaft with transition to metaepiphysis of the left femur, fixed by a plate, plate fracture, screws migration. This non-union belongs to group III (54 points) according to the Non-Union Scoring System (NUSS) [19], which is characterized by both a mechanical problem such as fragments fixation stability loss, and a biological problem such as compromised blood supply in the non – union zone. The patient was included in the clinical trial.

Radiography of the femur with the capture of the knee joint in standard anteroposterior and lateral projections and computed tomography were performed (Fig. 1).

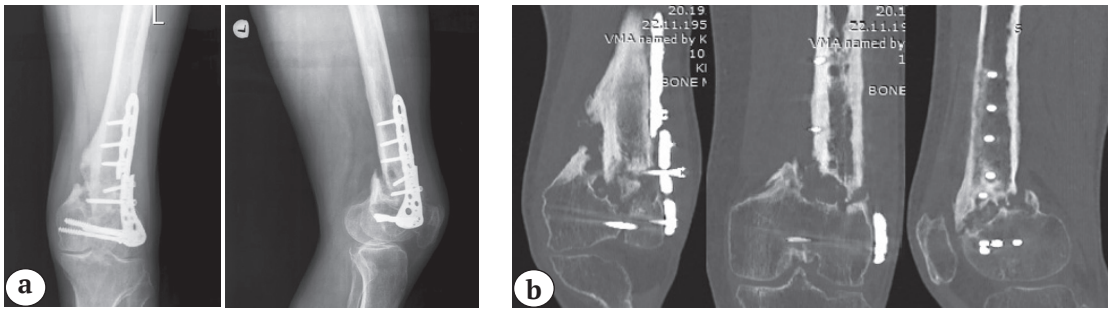

Figure 1. X-rays (a) and CT (b) of the distal femur: non-union with a bone defect of the lower third of shaft with transition to metaepiphysis of the left femur, fixed by a plate, plate fracture, screws migration

According to the X-rays, size of the suspected bone defect which required replacement after the correction of the position and resection of the ends of the fragments was determined, and amounted to about 8.5 cm^3, during the preoperative planning was chosen combination of bone autograft with the gene-activated material for filling up of the defect. The patient underwent removal of the metal implants, debridement of the non-union zone, reconstruction of the femoral bone defect, osteosynthesis with two plates.

Surgical technique

Patient in supine position, implants (plate and screws) were removed from the 10 cm lateral approach and the 8 cm medial approach in the middle and lower third of the thigh, scar tissue was removed. Resection of bone margins in the non-union zone, reaming of the medullary canal were performed. Bone defect was filled with the iliac crest two autografts 1.0x1.25x1.5 cm (3.75 cm^3), bone fragments from the non-union zone (about 1 cm^3) and 3.75 cm^3 of the gene-activated osteoplastic material "Histograft" in form of 0.5-1.0 mm granules mixed with the patient's venous blood (Fig. 2). The ratio of bone autograft and the gene-activated osteoplastic material was 1:1.

The fragments were fixed with a distal femoral locking plate using a minimally invasive technique (the proximal screws were inserted from individual skin punctures). Then, from the medial approach, mechanical stabilization of bone fragments and granules of gene-activated osteoplastic material was performed with a reconstructive locking plate (Fig. 3). The wounds were sutured in layers. The lower limb was immobilized by a splint. Postoperative radiography of the distal femur was performed (Fig. 4). The postoperative period was uneventful.

On the X-rays, fragments fusion was evaluated at 3 and 6 months using the REBORN scale (Table 1) [20, 21] using standard X-rays and computed tomograms. The medial and lateral cortical layers were evaluated on an anteroposterior X-ray and on axial and transverse CT sections. The anterior and posterior cortical layers were evaluated on a lateral radiograph and on the sagittal and transverse CT sections.

Figure 2. The gene-activated osteoplastic material mixed with the patient’s venous blood

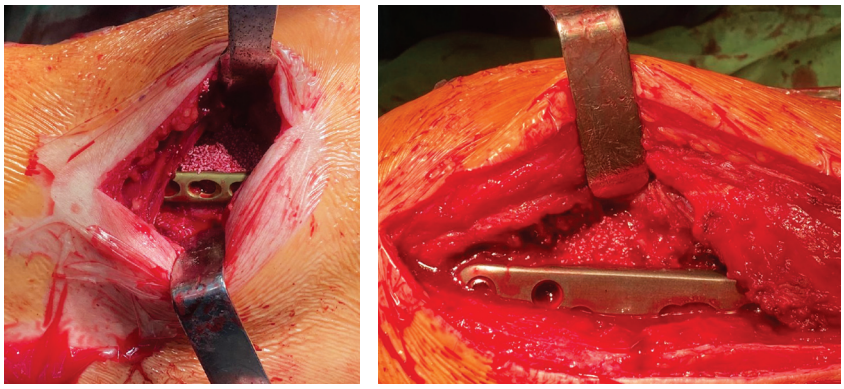

Figure 3. Femur bone fragments, granules of gene-activated material, bone autograft are fixed with plates

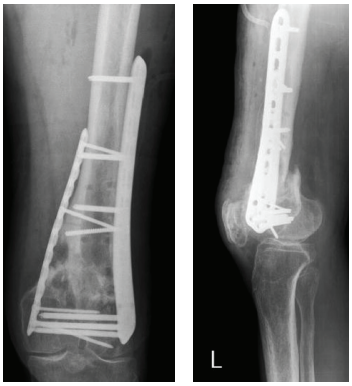

Figure 4. X-rays of the distal femur, fixed with two plates, the defects are filled with bone autograft and the gene-activated osteoplastic material in the ratio of 1:1.
The position of the fragments and the plates is satisfactory

Table 1

REBORN Consolidation Rating Scale

Points	Stage
1	Fracture site without changes *
2	Callus, but not continuous
3	Callus continuous, but fracture site still obvious
4	Callus with normal cortical layer density
0	Not visualized

* In comparison with the preoperative study.

The tomograms were analyzed using standard tools in the RadiAnt DICOM Viewer software [Medixant, Poland]. Evaluating the obtained tomograms images in axial, sagittal, and transverse projections, the density of the formed regenerate (in Hounsfield units, HU) was determined using the ROI (region of interest) tool, accurately positioning the ellipse in the autografts and "Histograft" granules area (Fig. 5).

The pain syndrome was assessed using the Numeric Rating Scale (NSR) during a control visit of the patient at 1.5, 3, and 6 months [22]. The function of the knee joint and the lower limb was evaluated by the Knee Society Score (KSS) [23].

For 3 weeks after surgery, immobilization was maintained with a special orthosis (splint) in the neutral position of the knee joint. The dosed load was resolved 3 months after the control computed tomography of the distal femur metaepiphysis (2 points on the REBORNE scale). After 6 months, control radiography and computed tomography revealed complete fusion (4 points on the REBORNE scale) (Fig. 6). The tissue density

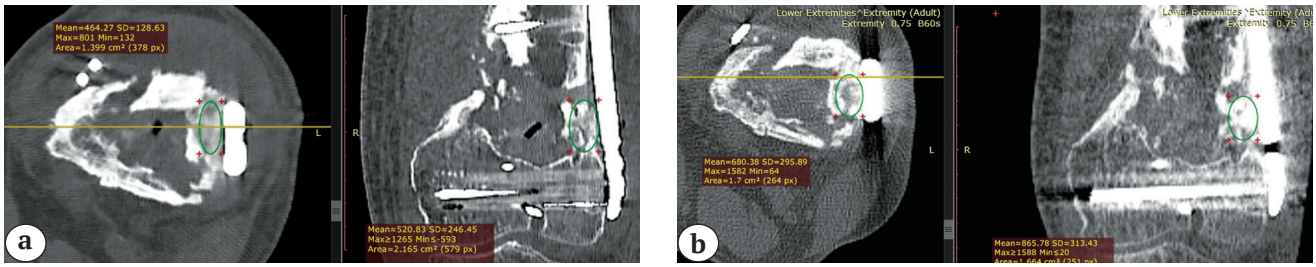

Figure 5. Interface of the working area of the RadiAnt DICOM Viewer program at the time of determining the regenerate density. The measurement area, ROI is highlighted:
a — density measurement immediately after the operation; b — 6 months after surgery

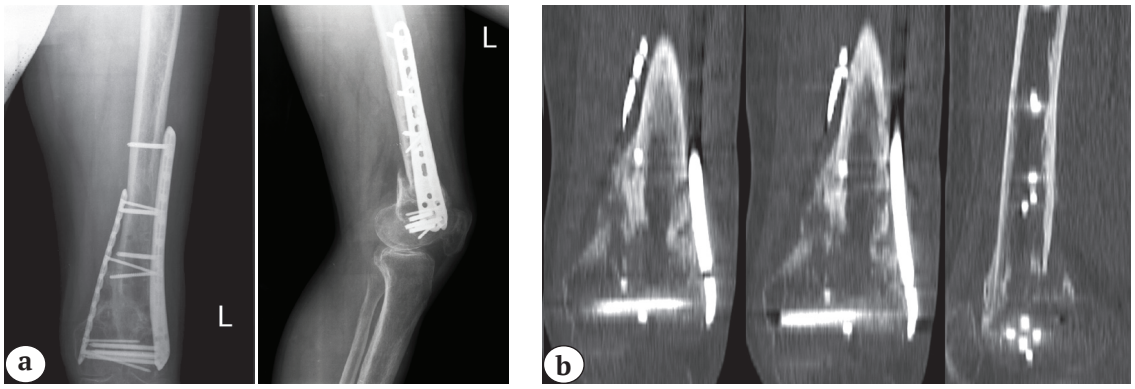

Figure 6. X-rays (a) and computed tomograms (b) of the distal femur: consolidation of fragments is determined

in the gene-activated osteoplastic material "Histograft" area after surgery was 521.2 HU. 6 months after surgery density was 867.7 HU. The positive dynamics in tissues density in the bone defect area caused by reparative osteogenesis was clearly observed.

Pain syndrome was practically absent (NRS-2). The range of motion in the knee joint: flexion - 80°. extension – 180°. According to the Knee Society Score (KSS) - 68 points. Thus, the effectiveness of the gene-activated osteoplastic material using for angiogenesis stimulation in the non-union zone is obvious.

Discussion

Treatment of distal femur non-unions is a challenge for orthopedic surgeon. Currently, published articles describe using of various implants with bone autografts [10, 24] or osteoplastic materials [9, 25, 26], confirming the lack of consensus on the optimal treatment of distal femur non-unions [1, 2, 3, 4, 5].

The most common treatment protocols for atrophic distal femur non-unions include using of structural autografts from the ilium and its fixation with a locking plate [10, 24, 27]. Variants of using multiple implants to increase the stability of fragments are also described [9, 27]. It is known that osteosynthesis with two plates in cases of unstable fractures of the distal femur is much more resistant to cyclic deformities [9].

In this clinical case, we performed fixation with two locking plates, and since the compromised blood supply and osteogenic insufficiency are critical factors in type III non-unions according to the NUSS scale [28, 29, 30], the gene-activated osteoplastic material with an angiogenic effect due to plasmid DNA with the VEGFA gene was used to stimulate angiogenesis of vascular formation in the atrophic non-union zone. Previously, this gene-activated material has been shown

to be safe and highly effective in jawbones grafting. The clinical study involved 20 patients with atrophy and defects of the alveolar ridge. 6 months after reconstructive surgery patients were determined to have bone density regenerate in the intervention area. Later, dental implants were placed in the regenerate area and trepanobioptates were simultaneously taken, which confirmed the formation of bone regenerate around the granules of the implanted gene-activated material [31].

To date, the most common "activating" components in clinical practice are growth factors, such as bone morphogenetic proteins (BMP-2, BMP-7) [36, 37], transforming growth factor beta (TGF - β1), vascular endothelial growth factor (VEGF-A) [32, 33, 34].

Vascular endothelial growth factor-A165 (VEGFA) plays key role in the development of angiogenesis, both physiological and pathological. Therefore, if a patient has cancer, it is not recommended to use a "Histograft", although the absence of a systemic effect with local administration of a drug based on plasmid DNA with the VEGF gene has been experimentally proven [35].

Some authors use activated materials "in pure form" [36], others in combination with bone autografts [10, 18, 24]. In particular, Hackl et al. achieved good results in the tibial and femoral shafts non-unions treatment (92.3% of fusion cases for up to 8 months) due to using of osteoplastic material containing bone morphogenetic protein-7 (BMP-7) in its pure form [37]. At the same time, in comparison with the control group, which included using of bone autograft, there was practically no difference. Allsopp et al., Kanakeshwar et al. also reported that the effect of bone induction with activated materials does not exceed bone autotransplantation [38, 39], and that materials with bone morphogenetic protein can lead to slower consolidation than the use of bone autografts, although the difference was not statistically significant.

The combination of osteoplastic material containing rhBMP-7 and bone autografts demonstrated high success rate of 92.6% in the treatment of atrophic long bones non-unions [40]. This fact confirms the possibility of using materials in combination with bone autografts.

Conway et al. compared the results of patients with long bones non-unions treatment using osteoplastic materials containing BMP-2 and BMP-7. The data showed that patients performed full axial load on the limb at an average of 15 and 23 weeks, respectively. In addition, fusion occurred in more limb segments in the BMP-2 group (93%) than in the BMP-7 group (70%) [41].

It is worth noting that using of osteoplastic materials with bone autografts combination in infected non-unions also proved its effectiveness, although the percentage of fusion was about 60% [42].

Conclusion

In this clinical case using the gene-activated osteoplastic material based on octacalcium phosphate and plasmid DNA with the VEGFA gene, complete fusion was achieved on 6 months period (4 points on the REBORNE scale). At the same time, no negative events were observed, which confirms safety and effectiveness of the product and allows further clinical research.

Ethical approval

The clinical trial protocol was registered in the international registry clinicaltrials.gov (NCT04705857).

Ethical approval for this study was obtained from local ethics committee of Kirov Military Medical Academy

Informed consent

The patient gave written informed consent for participation in this study and publication this clinical case

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