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SVF Therapy of Delayed Fracture Union in Patients with Multiple Combat Injury. Case Report

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SUMMARY

Delayed union of fractures is one of the most frequent complications in orthopedic practice, especially in polytrauma patients. With the development of new methods of regenerative medicine, including the use of adipose derived stromal cells as a component of the stromal-vascular fraction (SVF), new possibilities for conservative treatment of this problem have emerged. This article presents a clinical case of conservative treatment of delayed union of a radial bone fracture using local SVF injections. In the fracture space, SVF with PRP creates a pool of cells that could differentiate towards surrounding tissue, releases various inducers of tissue growth and, via an indirect chemotactic effect on receptors, mobilizes the body's own resources and creates conditions for angiogenesis and trophism in the injured segment. In the patient with delayed consolidation after SFV-therapy, progress in clinical and radiological dynamics was noted with complete healing within 7 months. The positive clinical result provides a basis for further study and implementation in practice.

Key words: radial fractures, stromal-vascular fraction, osteosynthesis, adipose derived stromal cells

BACKGROUND

Fracture non-union, pseudoarthrosis and delayed union are manifestations of a common problem, namely disturbed bone tissue regeneration after a fracture. The average rate of bone regeneration abnormalities after injuries to the extremities is 15-18% of patients [1,2]. Some authors argue that the percentage of patients with impaired fracture consolidation reaches 25% [3,4]. Considering the presence of multiple wounds in a large number of cases among military personnel, the problem of delayed fracture union becomes relevant due to the general severity of their condition and a significant load on the compensatory regenerative resources of the body. The presence of infection (combat injury: gunshot or mine-explosive, shrapnel, etc. – are considered contaminated by default), a significant amount of bone defects (lack of part of the bone, necrotic fragments that must be removed, etc., because of high energy damage), bone skeletonization (absence of surrounding soft tissues in many cases) and massive damage to the periosteum (impaired bone tissue trophism) are among the leading factors that give rise to complications of bone union. It should also be taken into account that, in severe cases, the treatment of bone fractures is limited to their fixation with external devices for patient stabilization, which delays surgery for stable osteosynthesis and increases the risk of complications. We should not forget about the severity of the victim's condition (presence of a combined injury, blood loss, shock, etc.), which requires the centralization of the body's resources to maintain vital functions, while bone regeneration, which requires significant electrolyte and mineral needs, does not receive those reserves, especially if multiple fractures are diagnosed. Bone union is considered to be delayed if there are no radiological signs of callus formation at the standard time for a specific fracture location, and clinically painful and rocking movements in the fracture zone persist [5-7]. Despite significant advances in the surgical treatment of patients with various musculoskeletal injuries, we still try to delay surgery using all possible conservative methods.

In modern traumatology, methods of regenerative medicine, including stromal-vascular fraction (SVF) therapy, have potential for use. The SVF freshly isolated from adipose tissue (AT) is used for tissue regeneration as it contains adipose-derived stromal cells (ADSCs). ADSCs are able to interact with their immediate microenvironment leading to the generation of new committed progenitors and cells. At the same time, they secrete exosomes containing growth factors, cytokines, chemokines, and micro-RNA involved in restoring tissue defects and biological functions. According to some reports, stem cells and progenitor cells in uncultured SVF constitute up to 3% of the total number of cells. Their use in therapeutic protocols depends on ensuring high cell numbers, low culturing passage, and reduced time delay before processing [8]. The efficiency of using the regenerative potential of MSCs in orthopedics is directly related to their quantity in the preparation. Based on this, confirmation of the quality of the cell preparation (qualitative and quantitative) is fundamental in obtaining the maximum positive effect. The SVF contains the cellular component, while PRP, in which the fraction is resuspended, contains growth factors (PDGF, CTGF, VEGF, IGF, TGF-β1 etc.) that are responsible for the restoration and formation of granulation tissue, cell growth in the human body [9-12].

CASE PRESENTATION

A 37-year-old male patient was admitted to the hospital as a result of being wounded during hostilities. The evacuation team took him to a stabilization point where he was examined by specialists, the first surgical treatment of the wound was performed, and he was referred for the next stage of treatment. On physical examination, in the topography of the distal third of the radius, there was an extensive, lacerated wound with uneven edges, areas of marginal necrosis, with bone fragments visible in the wound. Palpation revealed pathological mobility in the area of injury and crepitus of bone fragments. The function of the injured limb was absent due to severe pain. A neurological examination did not demonstrate any abnormalities of the peripheral nervous system. The vascular surgeon excluded peripheral vascular damage. The patient underwent an X-ray examination of the right upper limb in two projections, which revealed a complex comminuted fracture of the distal third of the radius with displacement of fragments.

Taking into account the clinical signs, history and instrumental examination findings, the diagnosis was an open fracture of the distal third of the right radius with displacement of fragments, S52.51 according to ICD-10 and 22-C3 according to Müller AO, Gustilo–Anderson Type II open fracture (Fig. 1).

External fixation was applied to the injured limb, while the wound was treated by negative pressure wound care (NPWC) method.

The skin defect was closed with skin grafting after the wound had healed. The patient was discharged to undergo rehabilitation on an outpatient basis. At a follow-up visit in 2 months, the external fixation was stable, the skin around the rods showed no signs of inflammation and the scar following skin grafting demonstrated no signs of necrosis or inflammation.

There was moderate swelling of the soft tissues in the area of the wrist joint. During the rehabilitation period, the patient reported intermittent severe pain in the fracture area that required a follow-up X-ray examination, which showed the absence of bone consolidation. A fracture at the stage of delayed union was diagnosed (M84.23 according to ICD-10 and 22-C3 according to Müller AO) (Fig. 2).

The decision was made to carry out surgical treatment by dismantling the external fixation, and performing an open reposition followed by osteosynthesis with an LCP (Fig. 3). The postoperative period was uneventful. The patient was discharged for rehabilitation. Calcium and vitamin D supplements were recommended.

At the next follow-up examination after 5 months, there were no radiological signs of bone fusion, and therefore a decision was made to carry out local injection SVF-therapy.

The patient received an injection of SVF in 4 ml PRP directly into the fracture area. PRP was prepared according to standard protocols by spinning twice to obtain a final preparation with a platelet concentration in the range of 3.7-4.1 times higher than the initial values. SVF was obtained from adipose tissue harvested from anterior abdomen and prepared according to a standard protocol. Written informed consent was obtained from the patient following a detailed explanation of the procedure.

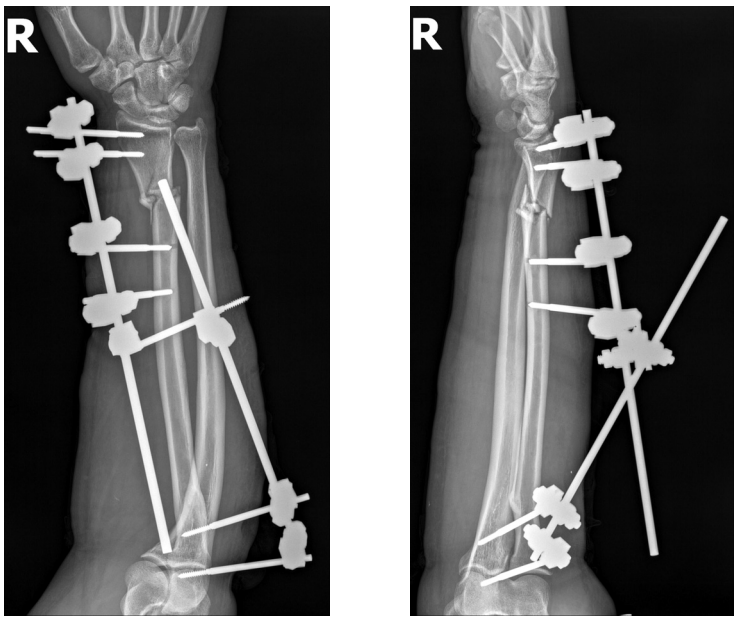

Fig 1. X-ray image of the injured limb with an external fixator on the first day of injury

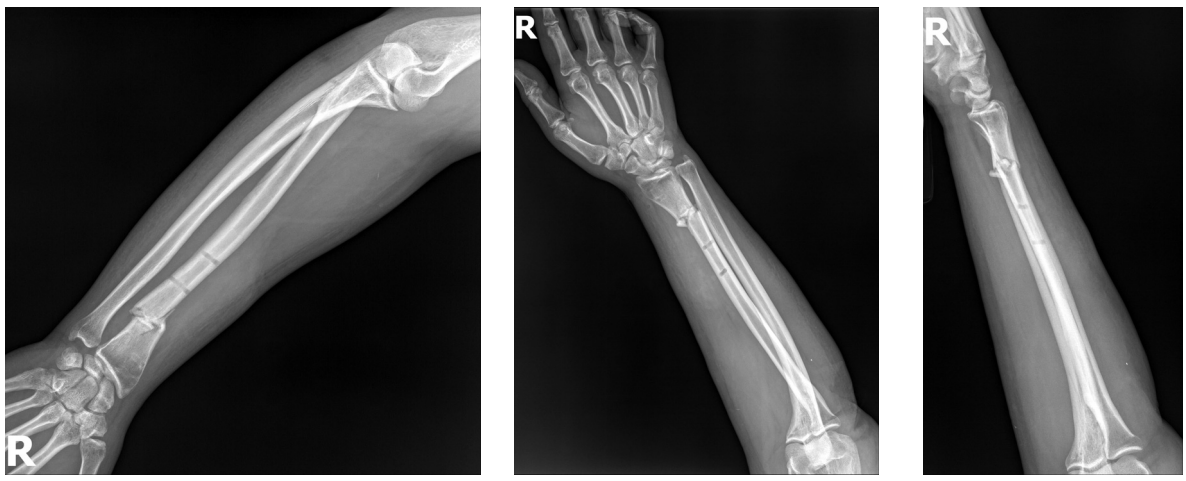

Fig. 2. X-ray image of radius fracture after removal of external fixator (2 months after injury). Radiological signs of delayed union of the fracture

The procedure was carried out in a sterile operating theatre under the guidance of a digital C-arm monitor. After careful analgesia, the patient was injected with SVF/plasma solution using a 16G × 3½ ‘’ needle into the fracture space, between the bone fragments. The injection was performed through one approach to several points with needling and damage to scar soft tissue conglomerates.

The patient was advised to continue conservative physiotherapy followed by X-ray 6 and 12 months

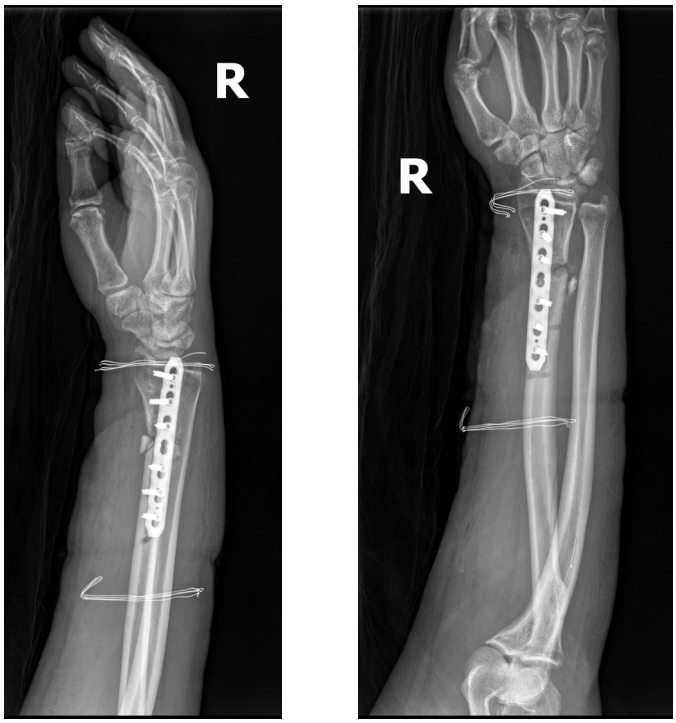

Fig. 3. X-ray image of a right radius fracture fixed with an LCP (4 months after injury)

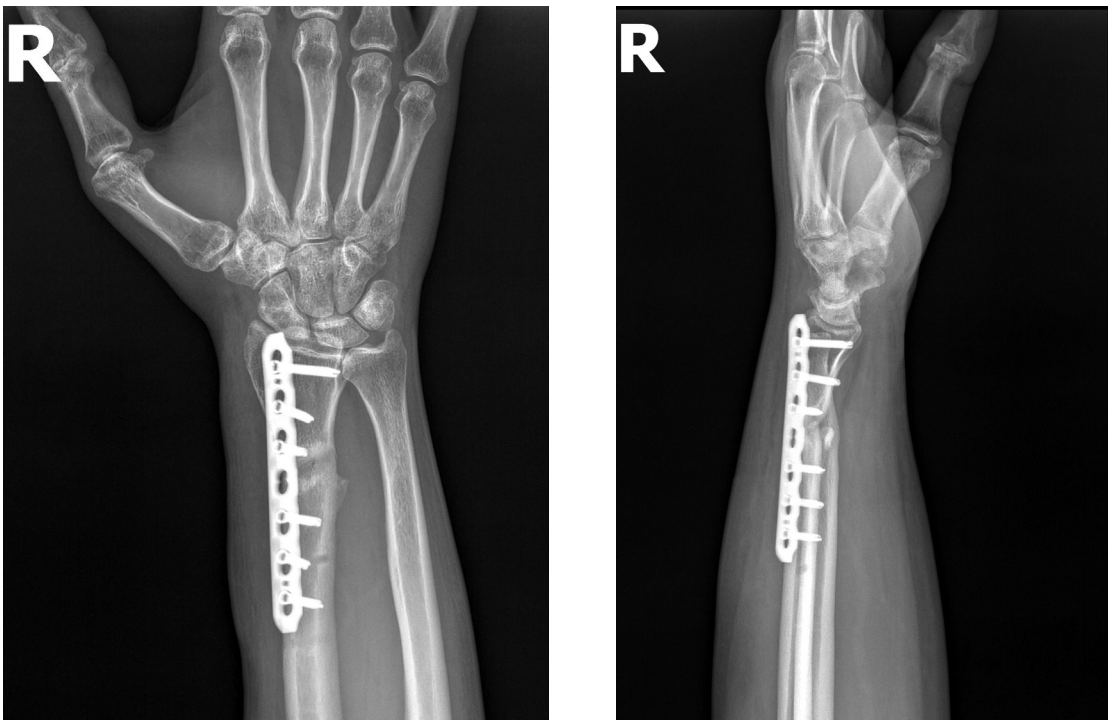

Fig. 4. X-ray image of a fracture of the right radius in the consolidation stage (6 months after injury). There are radiological signs of callus formation

after the procedure. Follow-up of the patient continued for 1 year after the start of therapy with clinical and radiological assessment of his condition.

During a pain assessment in 3 months, the patient noted a decrease in pain from 7 points to 5 points according to VAS. Radiologically, initiation of the consolidation process was noted in the form of the formation of a periosteal callus on the basis of fibrocartilaginous tissue.

Functionally, the patient notes an increase in the range of motion in the wrist joint.

After 6 months radiographically, the shadow of the periosteal callus was more than 2/3 of the circumference, which indicated the initiation of bone union (Fig. 4).

The patient returned to his military duties; no functional limitations were identified in the joints of the right upper limb. The patient notices pain only when performing significant physical activity.

DISCUSSION

Union of long bone fractures is undoubtedly a complex biophysical and biochemical process that requires significant resources from the patient`s body and consists of many links in the process "chain" that can be influenced to correct them. The process of bone repair depends on a number of local and general factors. The general factors include the patient's physical and neuropsychiatric condition, age, co-morbidities, endocrine system function, metabolism, nutrition, etc. However, in the vast majority of patients, non-union of fractures is mainly due to local factors. Initially, the location, degree of displacement of fragments and type of fracture affect the rate of union. The process of callus formation is significantly impaired if there is interposition of soft tissues covering the fracture surfaces or a large hematoma between and around the fragments, since all this interferes with the deposition of bone trabeculae between the fragments, which in turn inhibits fusion. Local metabolism of bone tissue, subcompensation or decompensation of cell proliferation due to impaired trophism, mineral depletion, etc., leads to an imbalance of the osteoblast and osteoclast cell pool towards the latter. The above factors can be influenced by stable reduction of bone fragments, careful revision of soft tissues in the damaged area and stable fixation using available methods of internal fixation.

This case report demonstrates that freshly-isolated SVF cells implanted directly into a bone fracture environment can form blood vessels and de novo bone tissue. It is known that the vascularization and vitality of bone fragments are of great importance for callus formation. As a result of the injury, vascularization and trophism at the edges of the fragments are affected to a greater or lesser extent. The periosteum in the area of the fracture is also damaged by injury and so it exfoliates and loosens. The more damage to the feeding vessels and periosteum, the less favorable the conditions for the fusion of fragments. The mechanical effect of needling and destruction of connective tissue scars in the fracture area causes local limited hemorrhage, which is a substrate for osteogenesis, and the additional administration of an increased concentration of mesenchymal cells with growth factors in plasma leads to the development of a local focus of multipotent low-differentiated mesenchymal cells that have the genetic potential to transform into cells of a certain type. It should be remembered that mesenchymal cells are not microscopic "naked spheres", but on their surface, they contain thousands of different receptors, thanks to which they perceive the environment they find themselves in and decide which way to differentiate. The ability to find the site of damage, or homing, is a natural ability of stem cells [13]. When the body has a large lesion that local stem cells cannot cope with, stem cells are sent to their aid from distant locations along a gradient of cytokines released from the damaged tissue or by a medical procedure. At the site of damage, the stem cell also continues to scan the situation through its receptors, which interact with a number of factors and finally make a decision: in this situation, it is enough to turn into a necessary cell once it is necessary to attract allies to fight [14-16].

In addition to the cellular component of therapy, platelet-rich plasma releases various inducers of tissue growth: FGF stimulates cell growth, synthesis of collagen and hyaluronic acid, VEGF is responsible for the growth and formation of new generations of vascular endothelial cells, TGF-β induces angiogenesis, etc. [17,18]. Activation and induction of regenerative processes promotes cell proliferation, angiogenesis and, as a consequence, fusion of bone tissue. Also, clinical experience shows that functional healing, taking into account normal activity, occurs long before normal intraosseous architectonics is restored, and may occur before maximum strength has been achieved.

SUMMARY

Local SVF therapy creates conditions for tissue repair and proliferation by activating the body's own regenerative capabilities including cell growth and differentiation, which is confirmed by clinical observations.

Local SVF therapy increases the concentration of multipotent cells in the damaged area, which minimizes the effect of a lack of the body's own resources for bone restoration.

Damage to the scar tissue in combination with the use of cell technology in the fracture area stimulates cell proliferation, angiogenesis, improves trophism and creates the basis for the formation of callus.

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