Percutaneous Autologous Bone Marrow Grafting on the site of Tibial Delayed Union
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Six months after injury, 150 mL of autogenous bone marrow was applied percutaneously at the site of delayed union to stimulate the healing of a tibial delayed union fracture in a 44 year-old man. Five months following the procedure, the fracture gaps and bone defects were completely filled with callus, the external fixator was removed, and the patient started using normal leg loading.

Key words: bone marrow transplantation; bone regeneration; callus; fracture healing; fractures, malunited; osteosynthesis, fracture

Bone healing is the result of a complex interaction of mechanic, molecular, and biological (cellular, local, and systemic) factors (1). While previously the significance and effect of systemic regulatory factors (hormones, vitamins, minerals, nutrition, systemic diseases) on cell elements was emphasized in the interpretation of the biology of healing, more recently the focus has been on the local regulatory factors which determine bone healing (transforming growth factor a and b, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factors, bone derived growth factor, interleukin-1, tumor necrosis factor, bone morphogenetic protein, prostaglandins). These factors derive from the bone cells, bone matrix or are synthesized by a variety of cells in adjacent tissue (2). Systemic factors can stimulate, suppress, or modulate the production of the local factors. Effect of the autocrine-paracrine factors on bone healing appears to be more significant than that of systemic factors (3).

According to the AO-Arbeitsgemeinschaft für Osteosynthesefragen (4), a fracture which has failed to heal after four months is referred to as delayed union, and as a nonunion after eight months. The nonunion is encountered in approximately 5% of fractures (5), while in open fractures healing disturbance rate is 15-20% (6). Frost (7) divided the causes of pseudoarthrosis into three groups: technical, biological (failure to make callus, inadequate regional acceleratory phenomenon, RAP, failure to mineralize callus, maldifferentiation, remodeling stage malfunctions, modeling stage malfunctions), and combinations of the two.

Currently, a number of methods are employed to deal with disturbances in fracture healing: stable osteosynthesis with intrafragental compression using dinamic-compression plates or intramedullary screws (4,8-10), bone grafts (4,11-13), microvascular bone transplants (14), electrical stimulation (15-17), and the Ilizarov method based on distraction osteogenesis (18-22). None of these procedures yield completely satisfactory results. They all require a complicated surgical technique, and are accompanied by high morbidity and numerous complications. Autologous bone grafting (spongioplasty) is one of the most common methods of treatment of non-union and smaller bone defects in spite of the 30-50% failure rate (23,24). The rate of successful healing of tibial pseudoarthrosis after autologous bone grafting is 70-95% (25). The method itself requires an additional incision at the transplant donor site, increases postoperative morbidity, causes weakness at the donor site, and is accompanied by many other complications (hemorrhage, hematoma, painful scar, infection, fracture). Chronic pain at the donor site is present in 25-61% of patients (26,27).

Bone marrow is the source of osteogenic cells (DOCP – determined osteogenic precursor cells) which are accountable for direct bone formation without the presence of additional stimuli (28,29). The source of osteogenic cells is the bone stromal system, which is defined as connective tissue elements within the bone marrow cavity, presenting the structural and functional support to hematopoiesis. Based on the morphology and the common origin, the bone marrow stromal system includes fibroblasts, reticular cells, adipocytes, osteoblasts, and bone-lining cells. Some authors also include macrophages and endothelial cells into the bone marrow stromal system, despite the fact that their source is different from that of other stromal cells (30).

We used autogenous bone marrow to stimulate the healing of a fracture in a 44 year-old man because of poor condition of soft tissues in the fracture region. Despite the high risk of complications during the wound healing period at the site of autologous bone graft application, we were motivated by numerous experimental studies (31-36), some clinical experience (37-39), and our own
Case Report
A 44 year-old man presented with a complicated, multi-fragmentary grade 3 fracture (AO grade) of the proximal tibial and fibular diaphysis sustained due to a fall of an electromotor onto his right lower leg. On the day of admission, debridement of the wound, fragments stabilization by external fixation, and fasciotomy due to the threatening compartment syndrome were performed. The position of the fragments on the postoperative radiologic examination was satisfactory. Dressing changes were performed daily accompanied by antibiotic prophylaxis (Kefzol 3x1.5 g, Garamycin 3x80 mg) during a 10-day postoperative period. The wound at the fracture site healed completely and without complications. Two weeks following the procedure, Enterobacter agglomerans was isolated from the fasciotomy wound, and was treated after antibiogram by Netilmycin 2x150 mg per day for 7 days. Twenty one days after injury, skin defect at the fasciotomy site was covered by a Thiersch skin graft. Thirty five days following the procedure the patient was discharged from the hospital to home care. At the follow-up examinations, the position of the fragments was satisfactory, with no changes compared with the first x-rays findings, however, with no signs of callus formation. As there were no signs of callus formation 6 months after injury (Fig. 1), we considered bone marrow grafting in order to promote the healing of the delayed union. A spongoplasty was excluded due to the poor condition of the soft tissues (adherent scar at the primary wound site, hypertrophic skin at the skin transplant site). Compared to autologous spongio- plasty, percutaneous autologous bone marrow grafting requires no additional incision at the bone marrow application site. The patient was informed about possible treatments and gave his consent.

Figure 1. Six months after fracture, no visible callus.

Figure 2. Six weeks after bone marrow grafting, newly forming callus is visible.

Figure 3. Five months after grafting, roentgenograms show healing of fracture.

Figure 4. Three months following the removal of external fixation, fracture gap and bone defect are filled with callus, no complications are visible.

The procedure was done under general anesthesia. Bone marrow was aspirated percutaneously from the iliac crest using a 3.0 mm needle. Three to five mL of bone marrow was obtained at a time. Simultaneously with the marrow aspiration, a second marrow needle was inserted into the site of the non-union. The adequacy of this position was assessed by fluoroscopy. A total of 150 mL of bone marrow was grafted, i.e., the surgical technique was identical to that described by Connolly et al (37). There were no postoperative complications either at the transplant donor site or at the bone marrow application site. Three days following the procedure the patient was discharged to home care. Postoperative radiological examinations performed every 6 weeks revealed obvious callus formation and a gradual filling of the bone defect with newly formed callus (Fig. 2). Five months after autogenous bone marrow grafting, the fracture gaps and bone defects were completely filled with a callus (Fig. 3). The external fixator was removed and the patient was able to walk with full weight bearing. During the 2-year follow up period after bone marrow application, no subsequent complications were observed (Fig. 4 shows the healing 3 months following the removal of external fixation).

Discussion
Bone marrow contains the osteoprogenitor cells that are important participants in bone formation and fracture healing. In 1934, McGaw and Harbin (41) were among the first to demonstrate the osteogenic activity of bone marrow. The work of Paley et al (34) showed that marrow produces optimal effects when used early in the fracture healing process, with the poorest results encountered when used in the treatment of non-unions. Successful healing in our patient agrees with the results obtained by Connolly et al (37) and Garg et al (39), who used percutaneous autogenous bone marrow grafting to achieve the healing of non-unions. Their results were the healing of 18 tibial nonunions out of 20 treated pseudoarthroses (37), and 17 healing of 20 non-united long bone fractures (39), respectively. Although percutaneous bone marrow injection does not promote healing more rapidly than would standard operative grafting, it has many distinct advantages over the latter. It is a relatively simple technique that can be done on an outpatient basis and, therefore, is cost-effective. The complications at the donor and recipient sites are significantly diminished (27,42,43). It can be done in cases that are not fit for open bone grafting because of the poor condition of the skin and can be repeated easily.
In the future, as stimulatory growth factors become available (44), the osteogenic effectiveness of marrow should be significantly increased by injecting it together with these factors. Ultimately, an injectable preparation that combines marrow with osteoinductive and osteoconductive agents should virtually eliminate the need for open harvesting and operative grafting as well as the problems associated with fracture healing (37).

References

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