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Clinical use of scaffold-technology to manage extensive bone defects

E.V. Kryukov[1], L.K. Brizhan'[1], V.V. Khominets[2], D.V. Davydov[1], Yu.V. Chirva[1], V.I. Sevastianov[3], N.V. Perova[4], M.I. Babich[1]

[1]N.N. Burdenko Main Military Clinical Hospital, Moscow, Russian Federation
[2]Kirov Military Medical Academy, Saint Petersburg, Russian Federation
[3]Federal Science Center of Transplantology and Artificial Organs named after V.I. Shumakov, Moscow, Russian Federation
[4]Institute of Biomedical Research and Technology, Moscow, Russian Federation

Introduction Practical application of regenerative medicine to restore structural and functional properties of damaged tissues and organs using bioactive implants could solve complex problems in contemporary traumatology and orthopedics. **Objective** To improve treatment results in posttraumatic diaphyseal defects of lower extremities. **Material and Methods** Treatment outcomes of 19 patients with posttraumatic bone defects of the femur and tibia that averaged of 8.8 ± 3.5 cm were studied. In the main group (9 patients), osteosynthesis of fragments was performed sequentially, first with external fixation and then with intramedullary nailing. Bone defect was bridged by a combination of a biomimetic tissue with a spongy autograft from the iliac wing. In the control group (10 patients), the Ilizarov method of non-free bone plasty was used. **Results** The results were studied after follow-up of two years. Bone defects were covered in all patients of both groups. However, in the main group, the physiological load on the limb was possible, on average, 7.6 months after surgery, which required 61 % less operations as compared to the control group. Also, the rate of complications was 29.2 % lower in the main group. When assessing the functional results using the LEFS questionnaire, the patients of the main group experienced some minor difficulties in performing physical activities, and patients in the control group experienced moderate difficulties (average score 70.3 and 50.4, respectively). **Conclusion** The combination of biomimetic tissue with a spongy autograft from the iliac wing under the conditions of stable functional osteosynthesis enables to manage extensive defects of the femur and tibia and improve the functional outcomes.
Keywords: bone defect, tissue engineering, scaffold, regenerative medicine, non-free bone plasty, osteoregeneration

INTRODUCTION

Scientific substantiation and worldwide use of the method of G.A. Ilizarov is the greatest achievement of domestic medicine. Management with this method is a “gold” standard for treating lower limb bone defects.

Bone defects are consequences of high energy injuries, bone infection, oncology and surgical aggression.

Preservation of lower limb function in such patients was guaranteed only by the use of extrafocal Ilizarov transosseous compression-distraction osteosynthesis and non-free bone grafting. However, its duration and outcomes of treatment does not fully satisfy both the patient and the doctor [1, 2].

On the other hand, internal osteosynthesis technologies may provide early functional recovery and lower limb weight-bearing. The two-step method of osteosynthesis of open fractures allows using the positive features of such treatment. At the same time, there remains the problem of bone defect bridging in the conditions of internal stable functional osteosynthesis [3, 4].

The attempts to combine intramedullary osteosynthesis and the Ilizarov method have not been widely tested for defect management. Search for optimal solutions to this problem continues [3].

Other attempts to manage bone defects were a combination of osteosynthesis with biopolymer materials, cell therapy, or prosthetics of the diaphysis with metal implants [1, 5–9]. All these techniques have not found wide or independent application.

Currently, the clinicians involved in the reconstruction of tissue defects focus on the possibilities of regenerative medicine, in particular, on the restoration of the structural and functional properties of damaged tissues and organs using bioactive implants [2, 10, 11].

A direction in tissue engineering and regenerative medicine which continues to successfully develop is the use of mimetic tissue (biomimetic material), which, like the extracellular matrix (ECM), provide the microenvironment (niche) for proliferation and

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differentiation of cellular components in the damaged tissues [2, 5].

A biopolymer microheterogeneous collagen-based hydrogel (BMCG) developed in our country and introduced into clinical practice is referred to such biomimetic materials. It comprises heterogeneous implantable gel from the class of bioactive hydrogel, mimetic of the extracellular matrix. BMCG incorporates almost all low and high-molecular components of ECM of animal origin, including biologically active molecules. This fact determines its pronounced ability to stimulate regeneration of various tissues, including the processes of angiogenesis and the migration of stem cells to the injury site [2].

BMCG possesses a developed structure of diffuse pores (from 200 to 400 μm), which allows cells to freely attach to the surface of microparticles of a cross-linked fraction of collagen, 200–360 μm in size. Cells adhered to the surface of BMCG produce components of their own ECM, which gradually replaces the resorbable BMCG and restores the structure and volume of tissues [2].

The aim of our work was to improve treatment results of managing defects in the diaphysis of lower limbs.

MATERIAL AND METHODS

We treated 19 patients with bone tissue loss throughout the diaphysis of lower limb long bones. All patients signed informed consents to be included into the study. The study was approved by the ethics committee.

We used the following classification criteria to characterize a bone defect: shape of bone loss (circular or marginal); length of the defect (small, 1–5 cm; medium, 6–9 cm; large, 10–19 cm; extra-large, over 20 cm).

All were males who sustained isolated fractures of the lower limbs due to exposure to high kinetic energy. Their average age was 27.4 ± 7.5 years. All fractures, depending on soft tissue damage, were classified according to the Gustillo-Anderson classification (1975) as type IIIa and type IIIb. All defects of the bone diaphysis were circular. Defects in 28.9% of cases had a primary nature, and in 61.1% resulted from initial surgical debridement of a wound at the previous stages of treatment. The length of the defects averaged 8.8 ± 3.5 cm (femur, 9.5 ± 1.5 cm; tibia, 8.1 ± 3.5 cm). On average, the severity of the condition in all patients as assessed on the scale of VPC-SP corresponded to the mild grade (27.5 ± 4 points). Combination of bone defect and nerve damage was an exclusion criterion. Multistage surgical tactics was used in the patients.

The patients composed two groups. The main group (9 subjects) was patients in whom bone defects were treated using the methods of regenerative medicine. In the first day after the injury, external osteosynthesis of fragments by various external fixation devices (AEF) was performed in this group. The principal conditions of this stage were the stability of fixation of fragments, the stiffness of the AEF construct, reduction of fragments, and preservation of limb length.

Musculoskeletal wounds were treated in parallel with measures to stabilize the general condition of the injured persons.

Once the soft-tissue wound tended to heal, the AEF was taken off and intramedullary nailing was applied. Such operations were performed on average after 17 ± 5.5 days post-injury (15.25 ± 2.5 days, femur; 21.8 ± 3 days, tibia).

To replace the bone defect, bone grafting was used in combination with the composition of a heterogeneous implantable gel SFERO® gel LONG (manufactured by BIOMIR Service, JSC). The autologous graft was bone chips (granules, 0.3–0.5 cm each), which were loosely laid in the area of the bone defect to contact with the metal structure and the ends of fragments. To optimize and stimulate the repair of bone tissue, 2 ml of an implantable gel was applied to the autograft implanted into the defect so that BMCG covered the bone defect along its entire extension. The wound was sutured in layers without drainage.

The operation of autologous plasty of a long bone defect with the use of a hydrogel matrix was performed simultaneously with AEF dismantling in two cases and a consistent internal osteosynthesis with a nail. In other cases, the implantable gel in combination with bone autoplasty was applied on average 22.7 ± 1.5 days after intramedullary osteosynthesis.

Bone defects in the control group were managed with the Ilizarov method. A circular wire-and-halfpin system for external fixation was used with two or more rings and arches and an intermediate ring in the bone defect area.

The Ilizarov method in this group of patients was the final method of treatment. Corticotomy with osteoclasia of the proximal fragment was performed on average 26.1 ± 7 days (29.6 ± 3 days for femur; 21.8 ± 2 days for tibia) after external osteosynthesis. Distraction of the bone fragment to bridge the defect was carried out at a fixed rate. Bone defect was filled in with a non-free graft with the formation of a distraction regenerate (period of distraction) on average for 130.6 days in the femur and 94.2 days in the lower legs. Later on, during the fixation period, measures were taken to "train" the regenerate.

The free bone autoplasty of the docking zone of the regenerate and / or the regenerate itself was used in 6 patients (three individuals with defects of the femur and three with the lower leg). At the same time, re-osteotomy of the fibula was performed.

All patients at the stage of regenerate formation were allowed limb weight-weighing (10–15% of body weight) and movements in the adjacent joints. After the regenerate had been formed, during the period of its adaptation, they were allowed up to 50% of their body weight, with a gradual increase in it to 4–5 months from the moment of the operation.

Clinical, functional and radiological results were studied on average after 2.5 years. To study the functional results, SF-36 questionnaires and a functional scale for lower extremities (Lower Extremity Functional Scale (LEFS), Binkley M. et al., 1999) were used. Statistical data were processed with Statistica 6.1 software. Student's t-test assessed the significance of differences between the groups. The differences were significant at a probability level of $p < 0.05$.

RESULTS

Treatment outcomes were studied in all patients of both groups two years after the end of treatment. In all cases, it was possible to achieve bone defect bridging and fusion of fragments.

There was a positive dynamics of early recovery of limb weight-bearing, fewer complications and good anatomical and functional results in all patients of the main group (Table 1). A comparative analysis of the effectiveness of the applied methods of osteosynthesis obtained significant ($p < 0.05$) differences in the results of treatment.

Inpatient stay of the main group patients was on average 2.3 times shorter and the number of interventions performed was on average 61.1% less than the number in the control group.

The functional load on the limb without additional means of support or using an orthopedic cane in the main group was possible 4.6 months earlier than in the control group (average 227.9 and 365.8 days, respectively).

The number of complications in the main group was by 29.2% less than in the control group. Contractures of the adjacent joints was the main complication in the groups which made 33.3% in the control group and 29% in the main group from the total of all complications. In the control group, this type of complication was detected in all patients. Also, 100% of patients in the control group had infectious complications associated with inflammation of the tissues around the AEF wires. Thrombosis of the superficial and deep veins of the extremity was detected in 44% of patients in the main group and in 78% of the control group.

The only type of complication, characteristic only for the main group, was disorders of a local sensitivity in the donor area (iliac region and upper third of the thigh) in two patients.

All complications, with the exception of contractures, were successfully managed and did not affect the final outcome of the treatment.

Table 1

Patients' functional outcomes (n = 19)

Parameters	Main group (n = 9)		Control group (n = 10)	
	Femur defect (n = 4)	Tibial defect (n = 5)	Femur defect (n = 5)	Tibial defect (n = 5)
Number of interventions	6	5.4	14.2	15.8
Functional support on the limb (days): with orthopaedic means of support / without any support	32.5 / 260.5	30 / 214.7	130.6 / 392.1	94.2 / 357.3
Inpatient stay (days)	231.3	115.8	415.8	382.8
Functional outcome SF-36 (PF) (points)	28 ± 1*	26.8 ± 2.5**	23.6 ± 0.5*	22.4 ± 1.2*
Functional outcome LEFS (points)	76.7 ± 2.5*	69.2 ± 5**	51.6 ± 3*	49.5 ± 5*

Significant differences in the groups in the individuals with femur defect (*) and tibial defect (**), $p < 0.05$

The study of functional results on Physical Functioning (PF) using the SF-36 questionnaire revealed a slight limitation of the functions of the lower extremities in both groups, but in the control group this indicator was decreased more (23.6 points for patients with femur injuries and 22.4 points for those with a defect of the tibia in the control group out of possible 30 points versus 28 and 26.8 points, respectively, in the main group).

A statistically significant ($p < 0.05$) improvement in the functional performance of various physical activities after surgical treatment in all groups was also observed using the LEFS questionnaire (20 questions, the maximum score is 80). It was revealed that patients of the main group experienced "minor difficulties" (72.2 and 68.4 points for femur and tibia, respectively), and patients in the control group experienced "moderate difficulties" (51.6 and 49.5 points, respectively).

Case # 1 Patient S., 27 years old Diagnosis: gunshot wound of the thigh with the formation of a primary bone defect 11 cm in size, limb shortening of 2 cm (radiographic absence of bone is over 9 cm, shortening of 2 cm, the total length of the femur defect is 11 cm) (**Fig. 1**). The patient was admitted on day 3 after injury, the fragments were immobilized with a monoplaner AEF, with type IIIa femoral fracture according to Gustillo-Anderson (1975). The severity of the condition at admission corresponded to the average grade (28 points on the scale of VPH-SP). The operation included wound debridement, reassembly of the AEF to a more stable circular system (**Fig. 2**). On the 14th day, AEF was converted to internal osteosynthesis with an intramedullary locking nail and defect area plasty with a combination of an implantable Spherogel gel and a free spongy autograft from the left iliac wing (**Fig. 3**). Soft tissue gunshot wound healed by first intention within 18 days. From the 20th day, the dosed loading on the limb was allowed and full weight-bearing after 6 months. X-ray monitoring after 6 months (**Fig. 4**). According to X-ray findings, the defect of the femur was filled in with a well-structured bone tissue. The result two years after surgery using the SF-36 questionnaires for PF was 28 points, LEFS was 76 points (**Fig. 5**).

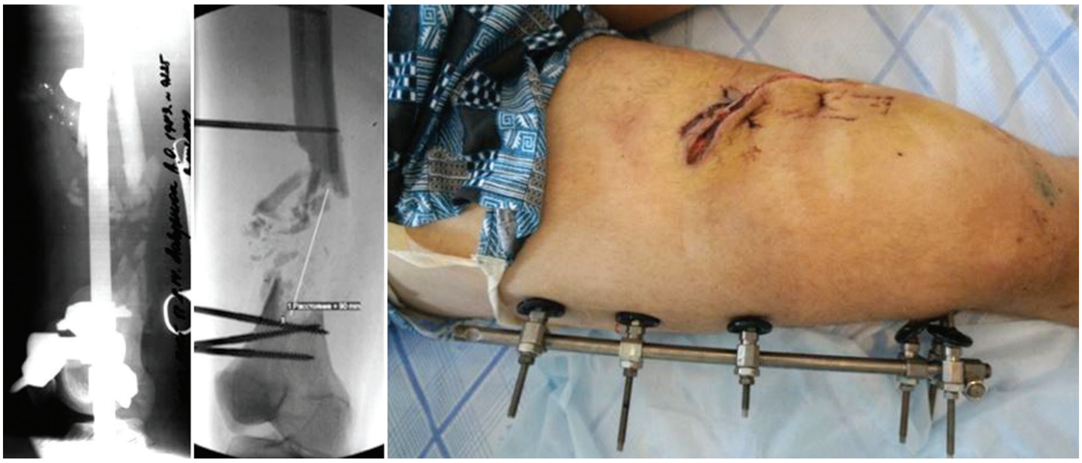

Fig. 1 Radiographs of the femur and the appearance of the thigh upon admission

Fig. 2 Radiographs and the appearance of the right thigh after wound debridement and AEF reassembly

Fig. 3 Radiographs of the right femur and the appearance of the limb after intramedullary osteosynthesis of fragments and bone defect plasty with implantable gel and autologous graft (14th day after injury)

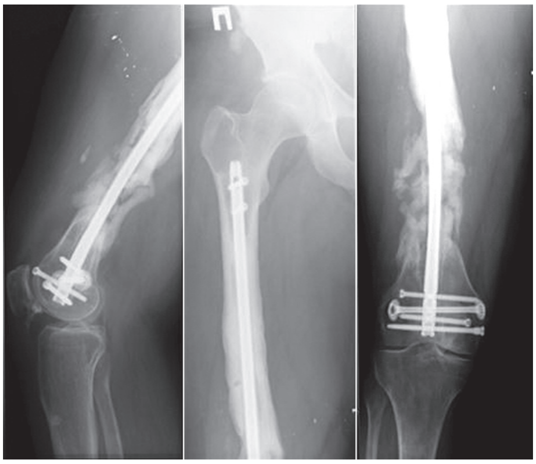

Fig. 4 Radiographs of the right femur of patient L., 27 years old, 6 months after the injury

Fig. 5 Anatomofunctional and radiographic outcome after 2 years

Case # 2 Patient H., 20 years old Diagnosis: gunshot injury of the left tibia at the border of the middle and lower thirds, 6-cm primary defect, lesions of the tendons of the extensors of the left foot (radiographic absence of bone over 5 cm, 1-cm shortening of the limb, the total length of the tibial defect of 6 cm) (**Fig. 6**); gunshot comminuted fracture of the talus of the foot of the contralateral limb was also diagnosed. Fracture of the left tibia of type IIIb according to the classification of Gustillo-Anderson (1975). The severity of the condition at admission corresponded to the average level (27 points on the scale of VPH-SP). Surgical debridement of the gunshot wound with immobilization of fragments in the circular wire-based AEF. The wound healed on day 23 (**Fig. 7**). The next intervention was dismantling of AEF, intramedullary osteosynthesis of the tibia with a locking nail, plastic repair of the tibial defect with a combination of a heterogeneous implantable gel and a free spongy autologous graft from the left iliac wing (**Fig. 8**). Postoperative period was uneventful. Dosed weight-bearing on the limb was allowed from day 14 after injury, full loading after 4 months. According to X-ray findings, the defect of the tibia was reconstructed by bone grafting and implanted gel, fragments consolidated after 6 months. The result the patient' 1.5 years follow-up with the use of SF-36 questionnaires showed PF score of 27 points, and LEFS was 68 points (**Fig. 9**)

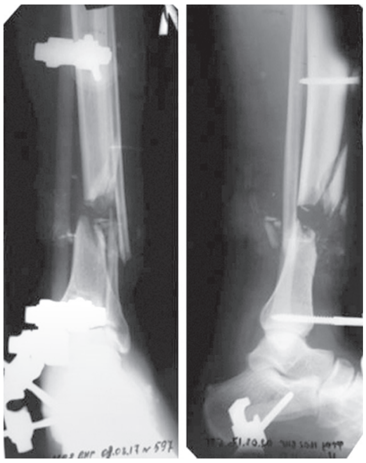

Fig. 6 Radiographs of the left tibia of patient K., 20 years old, upon admission

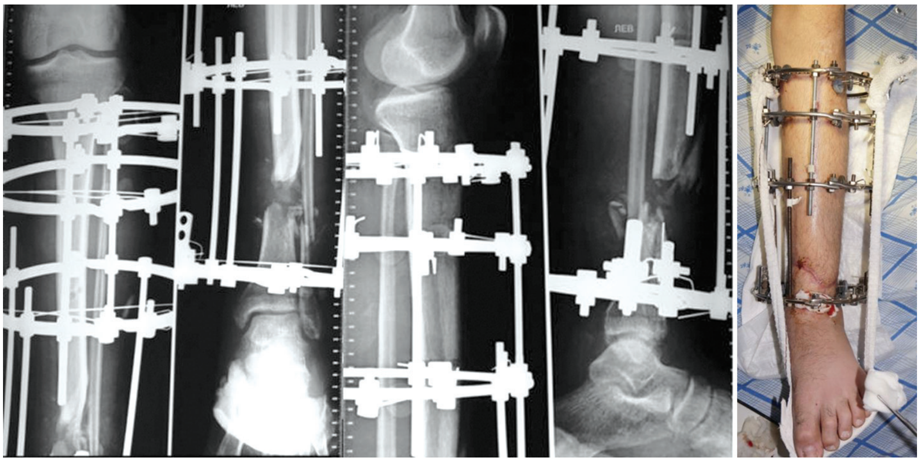

Fig. 7 Radiographs of the tibia and the appearance of the limb before conversion to intramedullary osteosynthesis and tibial defect plasty (24 days after injury)

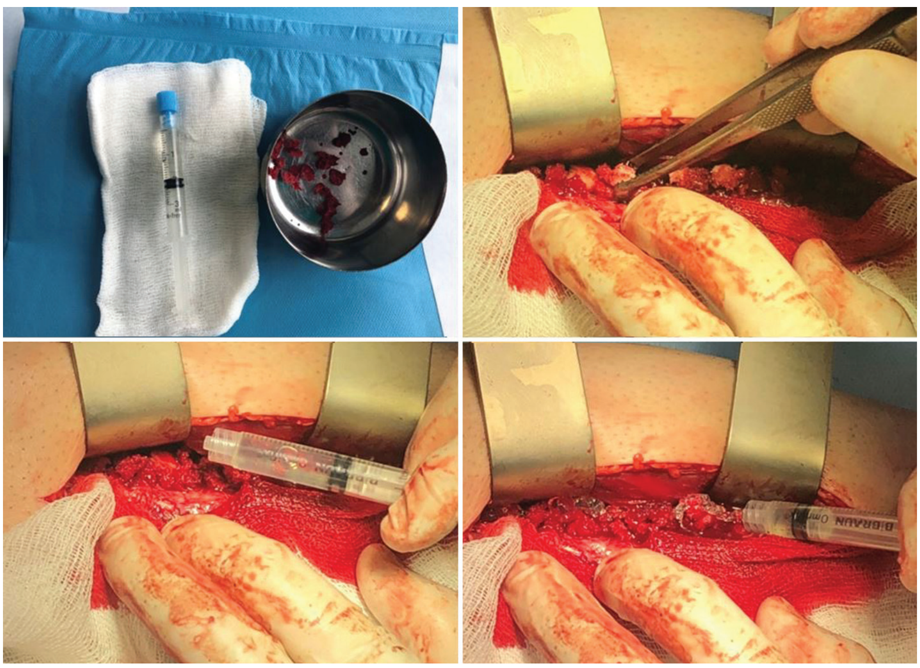

Fig. 8 Stages of the operation of bone autologous plasty in the tibial defect zone in combination with the implantation of a heterogeneous gel

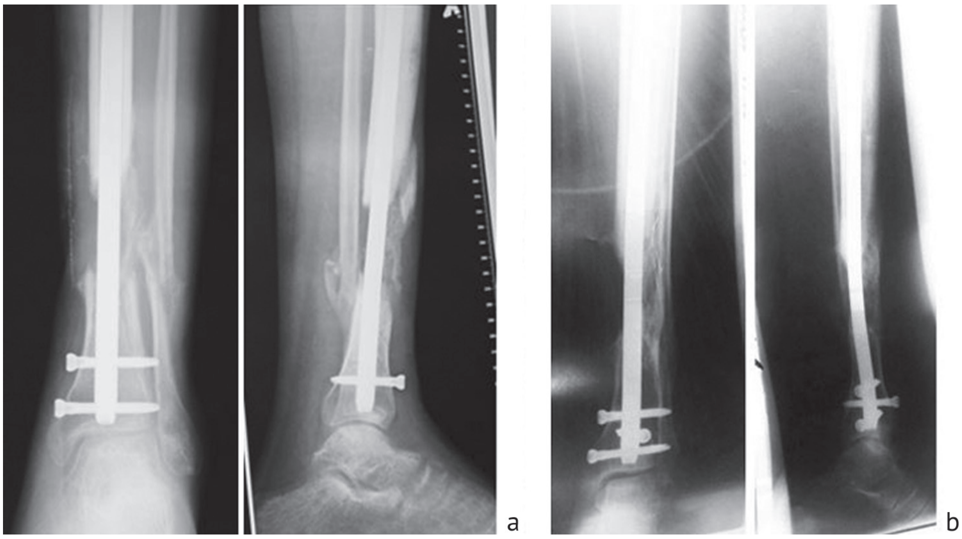

Fig. 9 Radiographs of the lower leg of patient K., 20 years old, 6 months (a) and 1.5 years (b) after the injury (images sent by the patient via the Internet)

DISCUSSION

Spongy bone autologous graft (SBAG) is a unique material in terms of regenerative medicine. It contains all the elements of bone tissue engineering: a sufficient amount of collagen and hydroxyapatite (matrix), all osteogenic cells (of various differentiation and specificity), as well as a sufficient set of mediators and of expressers of molecular signaling which provide bone remodeling. However, along with the well-known SBAG shortcomings (small amount, morbidity of the donor site), autologous grafting has another, a more significant drawback from the point of view of regenerative medicine, resorption ability. Resorption is a natural process. Osteogenesis is stimulated through the action of micromolecules and active substances of bone tissue resorption. However, the size of the bone tissue defect frequently exceeds the capabilities of osteoregeneration; and the process becomes incomplete and later turns to pathological (formation of a nonunion) [12].

The use of a matrix from a collagen-containing hydrogel, in our opinion, ensured the maintenance of the osteoreparation process that was started by bone autologous plasty, i.e. formed a working tissue-engineering scaffold, which later enabled bone defect filling in the mid-physiological period (average of 7.6 months). An important role is played by free-lying bone fragments and small fragmention in the process of osteoregeneration, as well as by the periosteum, which form bone trabeculae for connections and thus are integrated into a single bone regenerate [13].

Another important element of our approach to treating bone defects is ensuring new formation of the capillary network in the regeneration zone and an increase in tissue oxygenation necessary for the implementation and completion of osteoblastogenesis [14, 15]. This task was solved, first of all, by using the most stable and rigidly fixing systems of external and internal osteosynthesis. At the first stage of treatment, only a multiplanar AEFs with polyaxial half-pin insertion and/or circular wire-based systems were used for external osteosynthesis. In intramedullary osteosynthesis, the maximum diameter of the nails, bone canal reaming and locking into all technical holes for screws were used. Much attention was also paid to the treatment of integumentary tissues of the extremities for prevention of local infection process and to the general status of patients.

Another process that enables to form a solid regenerate and implement the Wolf's biomechanical law was the physiological load on the segment. It is known that microdeformation of the bone drives the periosteocytic fluid into motion and activates the transmembrane osteocyte receptors. Thus, the mechanical signals are transformed into biochemical ones and the mechanism of bone tissue remodeling is activated in general [16]. Further, by allowing the patients to bear weight on the limb which is splinted with intramedullary metal nail, the internal structure of the bone tissue adapted to the mechanical forces that it must withstand [14, 17].

In general, the use of internal stable and functional osteosynthesis contributed to the preservation of the functional state of the muscles and joints of the injured limb and to the correct walking stereotype in the injured persons that also influenced the results of treatment.

CONCLUSION

Given a small amount of clinical material and follow-up time, the technique presented requires additional study, but our experience allows us to draw some conclusions.

In our opinion, the combination of the matrix from a composition of the heterogeneous implantable gel from the class of bioactive hydrogel mimetic material with bone autoplasty could create an active and viable structure (scaffold) that provided bone defect filling.

Multistep surgical tactics, intramedullary osteosynthesis and the combination of tissue biomimetic material with spongy autologous graft from the iliac wing provide a physiological load on the segment and bone regenerate formation in the area of the defect of a lower limb long bone, on average, 7.6 months after surgery.

Such an approach to managing post-traumatic defects of lower limb bones that averaged 8.8 ± 3.5 cm is able to result in improved anatomical and functional treatment outcomes and reduce the number of complications in comparison with the Ilizarov method.

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Information about the authors:

1. Evgeniy V. Kryukov, M.D., Ph.D., Professor,
Corresponding Member of RAS,
N.N. Burdenko Main Military Clinical Hospital, Moscow,
Russian Federation
2. Leonid K. Brizhan', M.D., Ph.D., assistant professor,
N.N. Burdenko Main Military Clinical Hospital, Moscow,
Russian Federation,
Email: brizhan.leonid@mail.ru
3. Vladimir V. Khominets, M.D., Ph.D., Professor,
Kirov Military Medical Academy, Saint Petersburg,
Russian Federation
4. Denis V. Davydov, M.D., Ph.D., assistant professor,
N.N. Burdenko Main Military Clinical Hospital, Moscow,
Russian Federation
5. Yuri V. Chirva, M.D., Ph.D.,
N.N. Burdenko Main Military Clinical Hospital, Moscow,
Russian Federation,
Email: bf-4irva@rambler.ru
6. Viktor I. Sevastianov, Ph.D. of Biological Sciences, Professor, Honored Scientist of the RF,
Federal Science Center of Transplantology and Artificial Organs named after V.I. Shumakov, Moscow, Russian Federation
7. Nadezhda V. Perova, Ph.D. of Biological Sciences,
Institute of Biomedical Research and Technologies,
Moscow, Russian Federation,
Email: biomir-centre@yandex.ru
8. Mikhail I. Babich, M.D.,
N.N. Burdenko Main Military Clinical Hospital,
Moscow, Russian Federation