Review article
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Promising osteoplastic materials and surgical technologies in reconstructive treatment of patients with bone nonunion and defects

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Abstract

Introduction Some progress has been made in the development of innovative implantation materials for osteoplastic surgery. However, the problem of bone defect management still remains relevant due to the continued high prevalence of injuries resulting from road accidents, catatrauma, man-made disasters and military operations.

The purpose of the work was to analyze the relevant literature and to identify options for solving the problems of bone nonunion and defect management using materials developed on the principles of orthobiology and surgical technologies based on autologous repair.

Materials and methods The search for sources was carried out with the ConnectedPapers analytical tool and the capabilities of the eLibrary electronic library using keywords and without restrictions on publication date.

Results and discussion Recent publications contain information about the effectiveness of the combination of Masquelet technology and Ilizarov bone transport in patients with acquired and congenital defects, including in the conditions of active purulent infection. According to the literature, a promising autologous bone plastic material is the contents of the bone marrow cavity, containing osteogenic growth factors and bone morphogenetic proteins. Biomaterial is collected using the Reamer-Irrigator-Aspirator system (RIA) from the intramedullary canal of the femur or tibia. Currently, the effectiveness of bone morphogenetic proteins rhBMP-2 and rhBMP-7 in the restorative treatment of patients with bone defects and nonunion of various etiologies has actually been proven. The use of bone morphogenetic proteins has been introduced into foreign treatment protocols. Recent positive results of a combination of surgical technologies have proposed the combined use of the Ilizarov and Masquelet technologies, supplemented by PRP therapy. The basis for the expected effect from the combination of surgical technologies and orthobiological materials are the results of preclinical studies of the osteogenic potential of PRP therapy.

Conclusion There are grounds for studying the clinical effect of the combined use of surgical technologies based on autologous reparative processes and materials developed on the principles of orthobiology. It is necessary and advisable to clinically implement the use of bone morphogenetic proteins rhBMP-2 and rhBMP-7 in the reconstructive treatment of patients with bone defects and nonunion of various etiologies. Multicenter clinical studies of a high level of evidence are needed to determine the effectiveness of PRP therapy in the reconstructive treatment of patients with bone nonunion and defects.

Keywords: innovative implantation materials, osteoplastic surgery, bone defect, orthobiology, autologous reparative processes, Masquelet, Ilizarov, osteogenic growth factors, bone morphogenetic proteins, platelet-rich plasma therapy

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INTRODUCTION

Despite the progress achieved in osteoplastic surgery and in the development of innovative implant materials, there is no doubt about the relevance of the problem of bone defect management due to the consequences of injuries and high prevalence of injuries resulting from road traffic accidents, catatrauma, man-made disasters and military operations . According to most researchers, the optimal implantation material is still an autologous bone graft, but, unfortunately, the possibilities of osteoplastic surgery using free bone autografts are limited by the available donor material. The classical non-free Ilizarov plastic surgery and its variants when bone defect is treated by lengthening the fragment(s) are not without drawbacks. Basically, the opponents of the method stress its long treatment periods, loss of quality of life during external fixation and the risks of soft tissue inflammation in the area of transosseous fixation elements. The use of bone grafting according to Masquelet also has limitations in terms of indications for its use which is associated with long-term and incomplete organotypic massive implant remodeling, the risk of nonunion and pathological fractures, and infectious complications. At the same time, current literature contains information about the effective use of a combination of surgical technologies and autologous osteoplastic materials and products developed on the principles of orthobiology.

The purpose of the work was to analyze the relevant literature and to identify options for solving the problem of bone nonunion and defect management using materials developed on the principles of orthobiology and surgical technologies based on autologous repair.

MATERIALS AND METHODS

The search for foreign literature sources was carried out using an analytical tool based on artificial intelligence ConnectedPapers with the application of the Seminal works functions to display a list of key thematic works and Derivative works to display new, relevant works, systematic reviews and meta-analyses that are in the area of interest of the authors. A search for Russian-language sources was carried out in the eLibrary electronic platform with the keywords; the list was supplemented with publications from bibliographic lists, as well as with authors' own early publications. There were no restrictions on publication dates for selecting sources.

RESULTS AND DISCUSSION

Restoration of lost bone tissue in nonunion and defects is a key problem in reconstructive surgery and requires the use of innovative osteoplastic materials and new surgical approaches. It is known and generally accepted that the "gold standard" of osteoplastic materials are autografts. The literature review is devoted to the analysis of the results of the use and prospects for further improvement of autologous osteoplastic materials developed on the principles of orthobiology and surgical technologies to solve the problem of bone defect filling.

Non-free Ilizarov bone grafting (bone transport) is based on the fundamental scientific discovery "The general biological ability of tissues to respond to dosed stretching with growth and regeneration (Ilizarov effect)" (priority date: November 24, 1970, No. 355) [1].

The Ilizarov bone transport involves discrete and controlled movement of a blood-supplied autograft within a preserved soft tissue envelope in the interfragmental gap to fill the bone defect with newly formed bone tissue, which subsequently undergoes complete organotypic remodeling. The Ilizarov non-free bone grafting is able to recover the loss of any bone volume and completely restore the original anatomical shape of the bone segment that was injured [2–4].

Some authors use free autografts with arteriovenous shunting and non-free autografts along with the Ilizarov bone transport as alternative technologies and osteoplastic materials. Evaluating and comparing their effectiveness, researchers have not identified any fundamental advantages between these technologies in achieving anatomical and functional treatment results in bone defect repair [5–11].

The fundamental advantage of free and non-free autografts is their adequate blood supply and, accordingly, the possibility of union and complete organotypic restructuring of both the free replant after arteriovenous shunting and the transported bone fragment. Adequate vascularization of autografts ensures their resistance to infection, reduces the risks of purulent complications and ensures complete remodeling of bone tissue and the vascular network of implants [12–15].

The undoubted advantage of free bone grafting with blood-supplied autografts was the duration of treatment. In positive clinical outcomes, bone defect filling took place at once, and the union of the replant and recipient bone occurred in a time term close to the consolidation of uncomplicated fractures of an involved localization [7, 8, 14, 15–19].

A generally accepted and universal free blood-supplied autograft with a complex of tissues is the fibula with restored arteriovenous anastomoses [7, 12, 14, 17, 19–27].

At the same time, there is information in the literature about the effective use of the fibula as a free autograft, the role of the implant was performed by a resected fragment of the fibula. Organotypic restructuring of the fibula, remodeling of the newly formed vascular network, consolidation with fragments of the recipient bone occurred without surgical restoration of arteriovenous shunts [28–31].

The most favorable conditions for the reconstruction of the fibula are created when a free autograft was implanted into the zone of closed reaming of the medullary canal at the level of pseudarthrosis, when autogenous osteoplastic material was localized along the periphery of the reaming zone [32, 33].

The available literature contains information about the effective use of the fibula for total and subtotal defects of the tibia under the conditions of transosseous osteosynthesis. Reconstruction of the tibial skeleton is ensured by dosed tibialization or transport of the fibula into the defect area and formation of tibiofibular bone blocks and synostoses. The fibula plays the role of a non-free blood-supplied autograft, which undergoes complete organotypic restructuring. However, hypertrophy of the fibula and achievement of the strength characteristics of the tibia require dosed functional load and long-term use of additional immobilization means (plaster, splints, orthoses) [34].

However, free bone grafting with blood-supplied autografts has its own drawbacks. Typically, surgical intervention that is technically complex due to the need to use microsurgical techniques was two-stage: at the first stage of treatment, deformities and shortening of the segment were gradually corrected using transosseous fixation devices, a bed for the replant was prepared; transplantation was carried out simultaneously at the second stage of osteosynthesis. After a long microsurgical operation, there was a risk of thrombosis of arteriovenous shunts, which required the administration of expensive drug support. In case of blood-supplied fibula as an osteoplastic material, there was a risk of instability of the ankle joint in the donor segment, and a possible phantom pain in the donor area. In case of lower limb defect management

with vascularized autografts, the ability to substitute a missing bone part was limited by the amount of donor material available. As a rule, the bone autograft did not match the size of the bone defect; therefore, time was required for hypertrophy of the substituted bone tissue, long-term immobilization of the lower limb with orthoses, splints, and the use of additional means of support [12, 14, 16, 35–37].

Non-free Ilizarov bone grafting also features some problems. If the lengthening technology of the fragment(s) is incorrectly implemented, and first of all, if there is a traumatic violation of the integrity of the fragment(s) with damage to the contents of the bone marrow cavity and intraosseous artery, or an inadequate rate of non-free bone autograft transport, there are risks of an “ischemic” distraction regenerate of the hypoplastic type [38–42].

According to the literature, the slowdown in the activity of distraction osteogenesis and the risks of the hypoplastic distraction regenerates increase in one-stage lengthening or defect filling for more than 4–5 cm [43–46].

Highly appreciating the anatomical and functional results of long bone defect management by lengthening the fragment according to G.A. Ilizarov, opponents considered the main disadvantage of the method to be the long period of external fixation that impairs the patient's quality of life and determines the need for patient monitoring by medical staff [5, 47–51].

The need to reduce the duration and stages of treatment determined the evolution of the Ilizarov technology of non-free bone grafting with the development and implementation of new technological solutions. Thus, it was proposed to compensate for sub- and total defects of long bones with polyfocal distraction regenerates that undergo complete organotypic restructuring during a shorter period of external fixation.

The effectiveness of the methods for defect filling with polyfocal formation of regenerates has been proven by a 1.5-fold reduction in the duration of transosseous osteosynthesis and its stages (the distraction period is 2.5 times, the fixation period is 1.3–1.9 times shorter) with the achievement of greater completeness of bone defect filling within one treatment stage. At the same time, the fragments transported polyfocally retained vascular connections and were adequately supplied with blood, and therefore resistant to infection, and formed distraction regenerates underwent complete organotypic remodeling [44].

However, the proposed and implemented original technologies certainly increased the effectiveness of the Ilizarov non-free bone grafting but did not solve all the problems of reconstructive treatment of patients with defects and nonunion.

A promising autologous osteoplastic material is the bone marrow cavity contents harvested from the intramedullary canal of the femur or tibia using the Reamer-Irrigator-Aspirator system (RIA). Due to the widespread introduction of technologies for locked intramedullary osteosynthesis, minimally invasive approaches to the bone marrow canals are not technically complex and have been developed, and the amount of available donor material is quite sufficient to perform osteoplastic surgical interventions [52, 53].

Autologous bone plastic material contains osteogenic growth factors necessary to stimulate osteogenesis in areas with weakened bone tissue regeneration: fibroblast and platelet growth factors, bone morphogenetic proteins [53, 54].

According to some authors, the use of the Reamer-Irrigator-Aspirator system (RIA) is a promising and effective technology and can be an alternative or complement to the use of non-free bone autografts from the iliac wing [55, 56].

Despite the development of innovative implantation materials, the use of autografts is still the "gold standard" in osteoplastic surgery. Currently, there is a need to develop improved biomaterials based on the principles of orthobiology, and new technological solutions for implantation which would best meet the capabilities and in a number of characteristics would be superior to autografts. Innovative biomaterials can be combined with autoplastic material, resulting in the development of an implant that meets the requirements for osteoconduction, osteoinduction and osteogenesis [57, 58].

Recently, in the available literature there have appeared publications demonstrating high efficiency and identical results of the clinical use of the morphogenetic proteins BMP-2 and BMP-7 in comparison with autogenous bone grafts in orthopaedic correction of the spine and reconstruction of limbs after consequence of injuries [58, 59].

Congenital bone defects present the greatest difficulty for limb reconstruction, which predetermines multi-stage duration of treatment and high risks of disease relapse [60, 61].

Currently, foreign protocols for the treatment of patients with congenital pseudarthrosis include the use of bone morphogenetic proteins rhBMP-2 and rhBMP-7, with preference given to the use of autologous bone chips from the iliac wing as a scaffold [61–66].

It should be noted that orthopaedic surgeons give preference to transosseous osteosynthesis for fixation of tibial bone fragments, or to a combination of external fixation with intramedullary metal implants (intramedullary rods and bone plates) [11, 23, 60, 65, 67].

According to the literature, human recombinant proteins BMP-2 and BMP-7 are considered as osteogenic growth factors necessary to stimulate osteogenesis in areas with reduced bone tissue regeneration (congenital and acquired pseudarthrosis and bone defects, consequences of open fractures, osteonecrosis) [68, 69].

Bone morphogenetic proteins are thought to promote the chemotactic proliferation and differentiation of osteoblast and osteoclast precursors, thereby triggering the process of bone formation [66, 70, 71].

The lack of morphogenetic proteins in the domestic traumatology and orthopeadics is obviously due to their absent certification in the Russian Federation and cost (about $4500 for one clinical application). This fact should motivate researchers to search for clinically effective and financially accessible alternative osteoplastic materials and surgical approaches [72].

Non-free Ilizarov bone grafting and the filling of bone defects with autografts with arteriovenous shunting was recognized and developed in the 80s of the 20th century. At that time, A.C. Masquelet developed the induced membrane technique (IMT) [3, 4, 73].

The Masquelet technique involves reconstruction of the segment in two stages. In the first surgical session, a segmental bone defect is formed and a polymethyl methacrylate cement spacer is implanted. For fixation of the tibial bone segment, preference has been given to the Ilizarov apparatus. After 6–8 weeks, the spacer is removed, the defect is filled with free bone autografts, or in case of autograft deficiency, alloplastic implants are used [73, 74].

According to the literature, an induced membrane with a newly formed vascular network is formed around the spacer. The membrane contains mesenchymal stem and epithelial-like cells, fibroblasts, myofibroblasts, and produced morphogenetic proteins BMP-2, BMP-7 and growth factors (VEGF, TGF-beta 1) [74–76].

Peak levels of membrane-induced growth factor secretion were recorded at 4 and 6 weeks after spacer implantation [77].

In the available literature one can find information about the antimicrobial activity of the induced membrane, which is associated with the secretion of antioxidant chemicals by growth factors that caused the degradation of DNA microflora. The authors suggested the possibility of blocking the secretion of biofilm microorganisms by local peptides [78].

However, the Masquelet technology is not without its drawbacks either. Thus, the use of bone grafting according to Masquelet has limited indications, primarily in older patients, due to the low activity of reparative processes, and consequently long-term and incomplete organotypic reconstruction of massive implants, the risk of pseudarthrosis and pathological fractures, infectious complications, and problematic healing of postoperative wounds. [73, 79].

Lasanianos et al. conducted a comparative analysis of the treatment results of the Ilizarov bone transport (37 articles) and the outcomes of the Masquelet technique (41 articles). In the comparison groups, patients had similar sizes of bone defects. The researchers found that the results of surgical treatment using the Masquelet and Ilizarov technology did not have statistically significant and reliable advantages in restoring the anatomical integrity of the limb, formation of malunion, and the risk of infectious complications [79].

At the same time, a certain dissatisfaction with the results of surgical rehabilitation of patients using Masquelet bone grafting and Ilizarov bone transport prompted a group of authors to combine technologies in anticipation of optimizing the treatment process, reducing the duration and stages of osteosynthesis, reducing the risks of infectious complications, relapses of the disease while restoring anatomical bone segment integrity. The authors reported on the possibilities and effectiveness of the combination of Masquelet technology and Ilizarov bone transport in patients with acquired and congenital defects, including in conditions of active purulent infection [80–83].

With the application of the combination of Masquelet technology and Ilizarov non-free bone grafting, bone transport was carried out under favorable and optimal conditions for distraction osteogenesis. An induced membrane, which produces morphogenetic proteins and growth factors and also has bactericidal properties, was formed around the distraction regenerates and transported non-free autografts. As a result, bone defects were filled in with distraction regenerates undergoing complete organotypic restructuring, thus avoiding deformations and pathological fractures at the level of newly formed bone areas and reduced the risks of relapses of congenital pseudarthrosis and exacerbations of the osteomyelitic process [80–83].

The positive results obtained from the combination of surgical technologies enabled to develop the idea and propose the combined use of the Ilizarov and Masquelet technologies and supplement them with the use of orthobiological materials [84].

The basis for the expected effect from the combination of surgical technologies and orthobiological materials are the results of preclinical studies on the osteogenic potential of PRP therapy on cell cultures of human osteoblasts in vitro [85–87].

The results of the combined use of PRP therapy with osteoplastic materials seem promising. Thus, the results of creeping filling of a segmental defect of the tibia in experimental animals under the conditions of external osteosynthesis using an allograft with the addition of PRP were comparable to the results of autologous bone grafting. It must be emphasized that autologous bone grafting is still the “gold standard” and the reference osteoplastic material [88].

In the literature, there are optimistic results in meta-analyses of the experimental use of PRP therapy for low bone tissue potential to regenerate as an orthobiological material that stimulates histiogenesis [89–91].

A significant part of the work is devoted to studying the effectiveness of PRP therapy in combination with various orthobiological materials; therefore, it is difficult to associate the achieved results in the healing of nonunion and bone defect management only with platelet-rich plasma [91–93].

Thus, at the moment there is a need for works with a high level of evidence and reliable effectiveness of PRP therapy in the restorative treatment of patients with pseudarthrosis and bone defects.

CONCLUSION

The analysis of literature has shown that there are grounds for studying the clinical effect of the combined use of surgical technologies based on autologous reparative processes and materials developed on the principles of orthobiology.

Based, first of all, on foreign literature data, there is a need and feasibility for clinical trials on the use of bone morphogenetic proteins rhBMP–2 and rhBMP–7 in the reconstructive treatment of patients with bone defects and nonunion of various etiologies.

Currently, multicenter clinical studies with a high level of evidence are required to determine the effectiveness of PRP therapy in the reconstructive treatment of patients with bone defects and nonunion.

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