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Surgical treatment of children with extensive bone defects (Literature review)

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BACKGROUND: Reconstruction of extensive defects to bone tissue is one of the important problems of orthopedics and traumatology. Especially in acuteis, the problem is associated with the restoration of bone tissue in conditions of its deficiency in pediatric patients.

AIM: The aim of the study is to analyze modern methods of surgical treatment in children with extensive bone tissue injuries based on the published literature.

MATERIALS AND METHODS: Our report presents a review of the literature of methods of surgical treatment of extensive bone defects. The literature search was carried out in several databases such as PubMed, ScienceDirect, E-library, GoogleScholar for the period from 2005 to 2020, using the keywords given below. As a result of the search, 105 foreign and 37 domestic sources were found. After exclusion, 56 articles were analyzed, all presented works were published in the last 15 years.

RESULTS: The gold standard for replacing bone defects is still the use of autografts, including the use of technologies on a vascular pedicle. Various types of xenografts and allografts of bone tissue are increasingly being replaced by various kinds of synthetic implants.

CONCLUSIONS: To date, there is no single generally accepted standard for the surgical treatment of extensive bone defects. The option of surgical treatment of extensive bone tissue defects using tissue-engineered bone implants with axial blood supply seems to be extremely interesting and promising.

Keywords: extensive bone defects; pediatric traumatology; bone autografts; bone grafting in children; allograft; orthopedics; traumatology.

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Хирургическое лечение детей с обширными дефектами костной ткани (обзор литературы)

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Обоснование. Реконструкция обширных повреждений костной ткани является одной из актуальных проблем ортопедии и травматологии. Особенно остро стоит вопрос, связанный с восстановлением костной ткани в условиях ее дефицита у пациентов детского возраста.

Цель — проанализировать современные способы хирургического лечения детей с обширными повреждениями костной ткани на основе литературных данных.

Материалы и методы. В статье представлен обзор литературы, посвященный методам хирургического лечения обширных дефектов костной ткани. Поиск литературы осуществляли в базах данных PubMed, ScienceDirect, eLibrary, GoogleScholar за период с 2005 по 2020 г. по ключевым словам. Были выявлены 105 иностранных и 37 отечественных источников. После исключения проанализированы 56 статей, все представленные работы опубликованы в последние 15 лет.

Результаты. Золотым стандартом замещения костных дефектов по-прежнему остается использование аутотрансплантатов, в том числе с применением технологий на сосудистой ножке. Различные виды ксенотрансплантатов и аллотрансплантатов костной ткани все активнее вытесняются различного рода синтетическими имплантатами.

Заключение. На сегодняшний день не существует единого общепринятого стандарта хирургического лечения обширных дефектов костной ткани. Крайне интересным и перспективным представляется вариант хирургического лечения обширных дефектов костной ткани с использованием тканеинженерных костных имплантатов с осевым кровоснабжением.

Ключевые слова: обширные повреждения кости; детская травматология; костные аутотрансплантаты; костная пластика у детей; аллотрансплантат; ортопедия; травматология.

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ЭКО•ВЕКТОР

BACKGROUND

Congenital and acquired pathology of the musculoskeletal system is a significant medical and social problem. Currently, the number of patients with bone defects of various localizations is increasing [1]. The prevalence of orthopedic pathology ranges from 47 to 237 cases per 1000 children. Approximately 30% of cases of childhood disability are associated with congenital pathology and developmental anomalies of the lower extremities [2].

Causes of bone tissue defects are traumatic injuries and their consequences, congenital malformations, and destructive, infectious, and tumor damage to bone structures.

Bone defects of critical size are the most difficult clinical cases because they can lead to incomplete restoration or loss of function of the injured limb and ultimately disability. Such conditions often require bone transplantation [3]. Defects of critical size are defined as lesions, for which spontaneous healing is uncharacteristic. This indicator depends on age, anatomical area, type of damage, and many other factors; therefore, clear quantitative boundaries, especially for children, have not yet been determined [4].

Extrafocal osteosynthesis is one of the surgical treatment methods of patients with injuries of the musculoskeletal system, including those accompanied by impaired skin integrity and bone defects. Active research is currently undertaken on the use of a temporary fixation device in combination with promising and less-investigated implants and surgical techniques.

Recent studies have investigated the use of electrical stimulation to restore bone defects in the area of callus formation [5]. For this, three main types of electrostimulators are used: invasive, semi-invasive, and noninvasive. Stimulation by the cathode of the fusion site of the bone fragments within a certain range of current and its frequency has a beneficial effect on tissue regeneration. However, at present, electrical stimulation in clinical practice is still unclear [5].

Xeno-, allo-, auto-, and tissue-engineered grafts can be used as a biological material for filling extensive bone defects.

Bone tissue autograft remains the gold standard in the treatment of musculoskeletal defects [6, 7]. Rapid incorporation and consolidation in the absence of immunological reactions make the use of autologous bone the most attractive. The autograft has osteogenic, osteoconductive, and osteoinductive properties.

Xenografts are potentially capable of solving bone tissue deficiency with extensive bone defects, but their main disadvantage is the risk of developing an immunological response of the recipient to the donated graft [3]. In addition, the vascularization technique of xenografts is available. However, despite the urgency of the problem and active research in this direction, there has been no success in the use of this type of transplant in clinical practice [8].

Allografts are more widely used in comparison with xenografts, up to the transplantation of the upper extremities; however, with this option of replacing bone defects, despite modern methods of processing biological materials, there is a risk of transmission of human immunodeficiency virus as well as hepatitis B and C viruses. Thus, problems associated with allograft resorption and remodeling in the recipient's body remain relevant [9, 10].

The creation of synthetic materials, taking into account the physiological mechanisms of restructuring and remodeling of bone tissues, and development of engineered tissues led to the development of new synthetic implants used as osteoplastic material, including those with the possibility of additional implant colonization with stem cells [11, 12]. However, in most cases, these works are presented by experimental studies.

Moreover, tissue-engineered implants based on various materials using prefabrication methods [13] or vascularized with an arteriovenous loop (AVP) are highlighted. Such implants combine some of the advantages of vascularized allo- and autografts and artificial implants [14, 15].

This study aimed to analyze modern methods of surgical treatment of children with extensive bone damage based on the data available in the literature.

MATERIALS AND METHODS

This study presents a review of the literature on the methods of surgical treatment of extensive bone defects. The literature search was performed in the databases of PubMed, Science Direct, eLibrary, and Google Scholar for the period from 2005 to 2020 using the following keywords: "extensive bone damage," "Pediatric traumatology," "Bone autografts," "Bone grafting in children," "allograft," "orthopedics," and "traumatology." As a result, 105 foreign and 37 domestic sources were found. After exclusion, 56 articles were analyzed, and all of them were published in the last 15 years.

The following were the criteria for inclusion of articles in the study: full texts are available or structured annotations; clinical or experimental studies using bone replacement techniques; articles should contain quantitative data on the assessment of treatment results, its effectiveness, and safety; and authors, rating scales, and tests are indicated. Studies with signs of "duplication" were excluded (similar research protocol, similar groups and number of patients, similar group of authors, etc.). If a "duplicate" article was found, the most recent article in terms of publication date was selected.

RESULTS AND DISCUSSION

Spongy and compact autografts are distinguished. Spongy autograft is most often used in clinical practice, and it is characterized by high osteogenic, osteoinductive, and osteoconductive properties. Due to its porous structure, the graft can be completely vascularized within 2 days. Callus formation ends after 8 weeks, and a complete restructuring of the graft occurs within a year. This process is performed due to gradual replacement, defined as the simultaneous deposition of a new osteoid by osteoblasts and resorption by osteoclasts of the necrotic donor trabeculae. This type of graft provides fast fusion of fragments but does not create rapid structural stability [7, 16]. In most cases, traditional nonvascularized bone grafting is sufficient. In previously unsuccessful transplantation of nonvascularized bone, especially in infectious complications, vascularized bone graft is acceptable [17]. The most commonly used donor site for cancellous autograft is the ilium. Undesirable phenomena following autograft collection include severe pain in the area of graft removal, damage to the lateral cutaneous nerve of the thigh, hematoma formation, and infectious complications [3].

The autogenous compact bone cortical graft provides an osteoconductive conductive medium with minimal osteoinductive and osteogenic properties. It is used for structural defects that required immediate mechanical stability for healing. The dense matrix results in relatively slow revascularization and incorporation, as resorption must occur before the new bone can be deposited. This feature is the reason for the poor osteogenicity of this type of graft. Within the first 6 months after implantation, these nonvascularized autografts are resorbed, become weaker, but retain their structure [3, 7]. An autogenous cancellous compact bone graft offers the benefits of both bone types: immediate structural stability of compact bone and osteoinductive, osteoconductive, and osteogenic properties of the cancellous bone. Despite this, the donor resource for taking an autograft is extremely limited [16].

Surgical treatment with bone autograft does not require special equipment. Thus, it is necessary to ensure the aseptic condition of recipient tissues and maintain sufficient blood supply to the receiving bed. In the first days after transplantation, the transplanted fragments obtain nutrition through the diffusion of nutrients from the surrounding tissues; at a later stage, blood supply is realized due to the germination of blood vessels from the surrounding tissues. Autografts perform the function of an osteoconductor, slowly revascularizing. A free bone graft is less effective in reconstructive surgery than a vascularized one, since osteocytes die because pf insufficient blood supply and the graft undergoes partial resorption. In its place, a new bone is formed under the influence of pluripotent cells of the bone marrow and surrounding tissues [16, 17].

To improve consolidation, in some cases, autografts can be taken together with the vascular pedicle. Free vascularized grafts provide the most effective result and are indicated for large bone defects [16, 18, 19].

Vascularized grafts are traditionally taken from the iliac crest with its deep circumflex iliac artery, fibula with branches of the peroneal artery, distal end of the radius with the supraretinacular artery, or ribs with the posterior intercostal artery [6, 17]. More than 90% of osteocytes can survive, which makes this graft maximally osteogenic [16]. The donor areas for the collection of an autograft are extremely limited. With the transplantation of the graft on the pedicle, an additional limiting factor is the collection of the artery supplying a limited area, together with the bone. Insufficient blood supply to the bone will result in its partial resorption and decreased graft strength [20]. In a major review on this topic, Roddy et al. reported that the success of bone fusion after vascularized fibula transplantation ranges from 70% to 100%, and the average fusion time is approximately 6 months [3]. The rate of return to weight bearing and adequate functionality is also usually high at over 96% [3]. In contrast to an allograft, a vascularized autograft is actively involved in regeneration and provides an increased rate of hypertrophy and tissue fusion. Vascularized tissues have high resistance to infectious processes in comparison with nonvascularized grafts [6, 17].

Autotransplantation of vascularized bone tissues in the treatment of children has several salient points [7, 21, 22]. First, they are dictated by the possibility of further active growth of the length and width of the bone [21, 22]. One of the promising directions in this area is performing surgery on areas of epiphyseal bone growth, when restoration of articular function is required while maintaining the axial growth of the limbs. In such cases, conventional methods have several limitations, since they do not consider the disturbed nutrition of the epiphyseal plate, which leads with age to a progressive discrepancy in the length of the limbs [23, 24].

Thus, during the vascularized fibular epiphyseal transfer (i.e., transplantation of the vascularized fibular epiphysis), an area of the proximal fibular epiphysis is isolated with feeding legs that provide blood supply to the periosteum and endosteum, which supports epiphyseal growth [23]. Most often, the peroneal artery is used as the anastomotic leg (93%) and, in more rare cases, the anterior tibial artery [25].

In addition, autotransplantation of vascularized bone tissues in children are characterized with higher resistance to infections, increased spasticity of the arteries [21, 22], a low incidence of complications from the feeding pedicle due to the absence of age-related atherosclerotic and arteriolosclerotic changes in the vascular wall, and the absence of varicose veins in most patients [26, 27].

The characteristics and anatomical features of the fibula make it possible to use a vascularized autograft to replace almost any damaged bone. In particular, the isolated head of the fibula is used in the reconstruction of the shoulder joint [23, 25].

The bone growth plate can adapt the growth rate for different bones in pedicle autologous transplantation. This judgment is based on an earlier study of the growth rate of an autograft of the fibula during the reconstruction of tubular bones, i.e., 0.92 cm annually [23]. When transplanting a vascularized portion of the fibula to the calcaneus, the growth rate is 0.56 cm annually, which indicates a significant slowing down of the growth rate [28].

Autologous bone tissue transplantation surgery is at risk of complications. Early undesirable postoperative events include anastomotic leakage or thrombosis, neuropraxia of the deep peroneal nerve, and superficial skin infections, and delayed events include "late" anastomotic leakage, inconsistency in the length of healthy and operated limbs, graft fracture, flexion contracture of the limb, and ruptured skin necrosis over the surface of the autograft [25].

A systematic review of complications following transplantation of a vascularized fibula showed an overall incidence of early complications at the donor site (including infection, dehiscence, delayed wound healing) of 9.9% for wounds closed primarily and 19.0% for wounds requiring skin graft closure. Late complications include chronic pain (6.5%), gait disturbance (3.9%), ankle instability (5.8%), limited joint range of motion (11.5%), and sensory deficits (7.0%). In general, disadvantages of an autograft of the fibula include possible soreness of the donor site, extended operation time, fracture risk, especially of the lower extremities, and a complex microsurgical technique [3].

The technique for vascularized autograft is difficult, requires in-depth knowledge, and certain calculations for the formation of a musculocutaneous flap. Nevertheless, this technique can be the best option in the treatment of musculoskeletal pathologies in pediatric patients. Achieving long-term and necessary growth of the transplanted bone without its resorption is the most necessary parameter for children. Given the adaptive remodeling of the bone over time, this method can be used to replace almost any defects in the bone structure.

After surgery, graft viability should be assessed. The use of angiography for this purpose is not informative enough; even complete vascular patency does not indicate the viability of the graft. A more suitable option is to perform scintigraphy with technetium (Tc-99)-active accumulation of the radiopharmaceutical agent in the graft area indicates sufficient blood flow [29].

A bone graft at sizes >6 cm needs vascularization. In a systematic review by Allsopp, researchers tried to challenge this thesis [30], but as arguments, they cited insufficiently statistically reliable outcomes and limited research on this issue. These studies did not reveal the advantages of vascularized autografts over nonvascularized ones [30]. However, several researchers, whose work was not included in this systematic review, disagree. The advantages of vascularized autografts are evident in the treatment of children, when continued bone growth is possible [7, 22].

In addition to various transplantations types, various implants are used in the treatment of musculoskeletal diseases, such as the use of synthetic materials covered with stem cells [11, 12], composites based on hydroxyapatite [31], implants based on porous ceramics [32], and titanium and titanium alloys [11].

Such implants are greatly compatible with the recipient's tissues, less traumatic, and relatively easy to use [11, 31, 32]. However, synthetic implants do not possess the properties of biological tissues, namely, the ability to grow and develop, which is important in the treatment of pediatric patients. In addition, their physicochemical properties are not completely identical to native bone tissues.

Potentially, the success of autotransplantation of bone tissue and the reduction of complications can be achieved

Table 1. Local and systemic factors affecting the success of bone transplantation (according to Khan et al. [7])

Factors	Positive	Negative
Local	Mechanical load Mechanical stability Electrical stimulation Large contact area Growth factors	Mechanical instability Wound infection Radiation Denervation
Systemic	Vitamins A and D Thyroid and parathyroid hormones Growth hormones Insulin	Corticosteroids Nonsteroidal anti-inflammatory drugs Chemotherapy Smoking Sepsis Diabetes Malnutrition Metabolic diseases of bone tissue

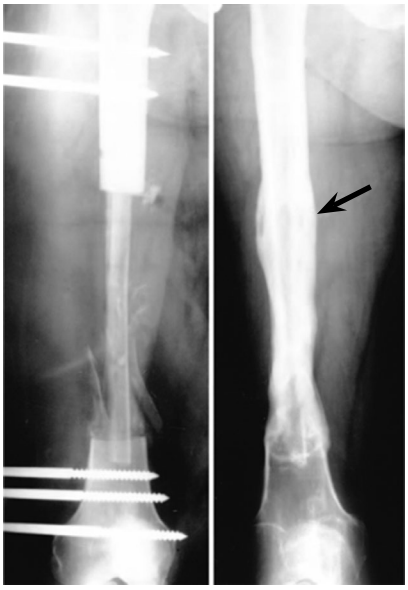

Fig. 1. Radiographs of a vascularized fibula autograft at the site of the femur defect immediately after surgery and after 9 months (the red arrow indicates the line along which the graft was incorporated) [29]

by addressing contributing factors (Table 1) [7]. Thus, several researchers argued that in the postoperative period, the use of nonsteroidal anti-inflammatory drugs and glucocorticoids is undesirable, and the parallel administration of radio- and chemotherapy significantly increases the consolidation time of bone autografts [3, 7].

Another factor that can have a positive effect on bone autograft is the level of mechanical stress. According to Wolf's law, the bone adapts to stresses. With an increasing load, the trabeculae are involved first in the restructuring, followed by the cortical layer, which leads to a compaction of the structure and a subsequent increase in bone strength. With a decrease in load, the bone tissue degrades, becomes looser, and its strength decreases [26].

Vascularized grafts undergo the same adaptation and remodeling as the native bone [26]. Given this property of bone tissue, with appropriate load on the graft, the grafted bone can grow in thickness to the size of a normal bone (Fig. 1) [26, 29].

Reconstruction of tissue defects using various tissue-engineered materials is a promising technique and an alternative to auto- and allotransplantation [14]. A study described successful experience of using tissue-engineered implants of the skin, urethra, blood vessels, flat bones, and cartilage tissue [33]. These tissue-engineered implants have one thing in common –they are thin, which facilitates diffusion of nutrients and oxygen. The situation is completely different with larger implants because thicker implants do not allow diffusion of nutrition [34]. Such implants require additional axial blood supply [14], especially immediately after their placement in the target area [35, 36]. A variant of such a blood supply is feeding the graft with a blindly closed arteriovenous bundle, a through arteriovenous bundle, or a shunted AVP [14, 37, 38] (Fig. 2). The most effective technique, according several studies conducted by Tanaka et al., is the use of an AVP; this alternative had the highest rate of implant vascularization [39]. The key factors for neoangiogenesis were hypoxia [33, 40] and turbulent blood flow in the anastomosed region, stimulating the production of connexin 43 [41].

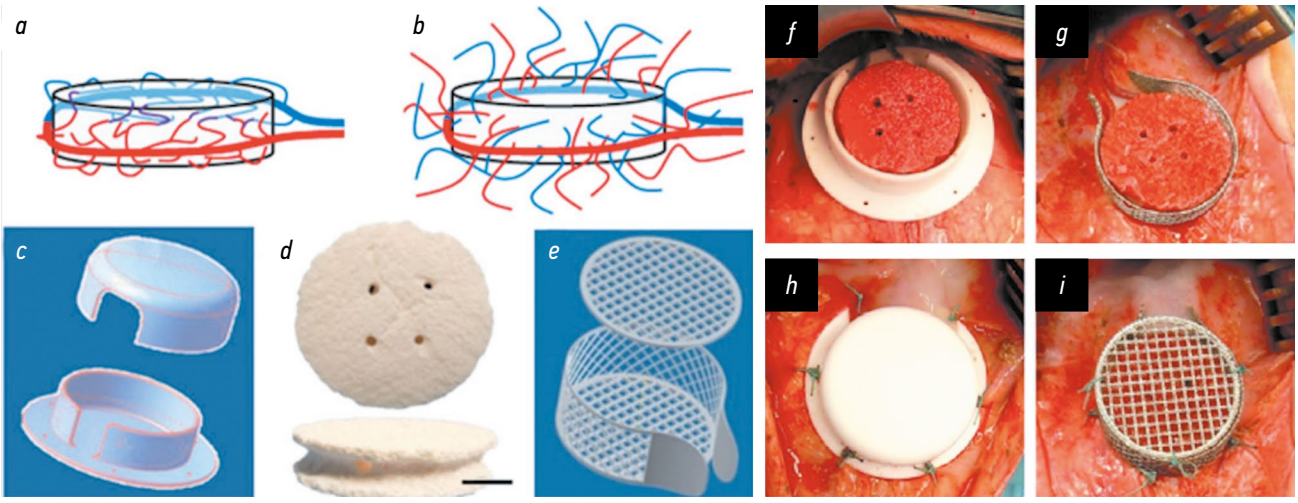

Fig. 2. Cameras used by Weigand et al. [38]: *a,* vascularization of the graft from the arteriovenous loop in a completely isolated chamber; *b,* vascularization of the graft from the arteriovenous loop and from the surrounding tissues in a perforated chamber; *c,* general view of a continuous Teflon polymer chamber; *d,* general view of the matrix made of NanoBone material; *e,* general view of a perforated titanium chamber; *f,* general view of a continuous chamber with a matrix and an arteriovenous loop located inside (the lid is open); *g,* general view of a perforated chamber with a matrix and an arteriovenous loop placed inside (the lid is open); *h,* general view of a continuous polymer chamber with a matrix and an arteriovenous loop located inside (the lid is closed, the chamber is fixed with sutures to the surrounding stitches); and *i,* general view of a perforated chamber with a matrix and an arteriovenous loop placed inside (the lid is closed, the chamber is fixed with sutures to the surrounding tissues)

For the first time, the technique of providing blood supply through AVP formation was proposed by Erol and Spira (1980). They successfully used this method to provide nutrition for the free skin flap [14]. Lokmic and Stillaert (2007) published their results of an experiment to create an AVP in an isolated polymer chamber. As a result, a fibrin clot formed around the AVP, which, gradually growing by arterioles and venules, was subsequently replaced by viable connective tissue [33].

Kneser et al. (2006) published the results of an experiment on artificial vascularization of a sample from processed bovine cancellous bone (PBCB) in an isolated chamber. For 8 weeks, the sample germinated with vessels, and connective tissue was found in the pores [14]. Other authors have described their experience of injecting a gel containing osteoblasts into a PBCB matrix and a gel containing vascular endothelial growth factor and basic fibroblast growth factor into fibrin matrices [42]. Osteoblasts survived for some time in PBCB matrices, but they were soon replaced by connective tissues. The authors explained that this was due to an increased reaction to the foreign structure of the PBCB; therefore, they suggested using other biocompatible materials that cause a lower formation of a connective tissue capsule as well as osteotropic growth factors [43].

Beier et al. (2010) published results of their experiment in which the AVP was immersed in a chamber filled with a composite of ceramic granules, fibrin, hydroxyapatite, and calcium phosphate. Computed tomography and histological examination revealed active vascularization of the composite by 12 weeks, but without the bone tissue formation [44]. In 2014, the same authors presented the successful application of the technique with the addition of autogenous cancellous bone and growth factors in two patients with extensive defects of the tibia and radius after osteomyelitis. At 36 and 72 months after surgery, the patients had bone formation at the site of the defect with full AVP patency [45].

However, none of the above options of using AVPs in an isolated chamber resulted in the formation of full-fledged bone tissues [43, 44, 46]. Osteoblasts [43] and mesenchymal stem cells [45, 47] were used to induce the bone tissue formation in the chamber; for their differentiation, it was recommended to introduce various factors into osteogenic cells (e.g., bone morphogenetic protein-2 [BMP-2]) [46–48] with sustained release [49].

A group of scientists managed to obtain full-fledged cancellous bone tissue in 2012 in an experiment on sheep. AVP was immersed in a matrix of β-tricalcium phosphate in combination with hydroxyapatite granules, injected with a medium with mesenchymal stem cells and recombinant BMP-2 [50]. The MSC and BMP-2 combination has been used previously [Jones et al. (2006) used a collagen sponge as a matrix]; however, with to the lack of an isolating chamber, the newly formed bone had an irregular shape and fused with the surrounding tissues, which created additional trauma during its release [51].

At present, prefabrication of a bone implant is another method is successfully used in clinical practice [14], which is not inferior in terms of the effectiveness of AVP. The future implant is temporarily placed in the thickness of soft tissues for vascularization from the surrounding tissues; after a certain period, it is removed and placed in the target area. Thereafter, the germinated vessels in the thickness of the implant are sutured with the surrounding vessels. However, this method has drawbacks: the submerged implant quickly becomes overgrown with connective tissues, which can prevent further growth of the target tissue [15]. Weigand et al. combined these techniques using perforated titanium rather than a continuous polymer chamber (Fig. 2). As a result, there was rapid vascularization of the graft without significant invasion of connective tissues [38]. To solve this problem, a modified guided bone regeneration technique was also proposed, which consists in creating a temporary mechanical barrier from a biodegradable membrane (50% poly(lactic acid)/50% polycaprolactone [PLA/PCL]) between the future implant and the surrounding tissues. The implant was fed by axial blood supply and partially by diffusion through the membrane. Then, the implant grew with new vessels, i.e., branches of the axial bundle, while there was no replacement with connective tissue from the outside [52].

In experimental studies on rabbits, Eweida et al. used subcutaneous vessels [53], and Dong et al. used the popliteal artery and anastomosed it with the femoral vein [13]. In other studies, researchers used larger animals and varied locations of the chamber with the implant [44, 48].

The most common complication, regardless of the animal or location of the chamber, is AVP thrombosis [54]. For its prevention and treatment, several authors recommended the use of anticoagulants and antiplatelets in the postoperative period [41, 55].

In summary, in most works, continuous cylindrical chambers made of polymer material (Teflon [14] or polycarbonate [33]) have been proposed. In some works, membranes made of expanded polytetrafluoroethylene [56] and PLA/PCL copolymer [52] were used. In some studies, a camera was not used [15]. Some authors used perforated chambers made of Teflon [37, 53] and titanium [38] instead of solid ones. In most cases, natural coral [56], b-TCP [15], PBCB [14, 42, 43], and composite materials [44, 50] were used as materials for matrix fabrication.

The results in most cases were assessed using the following techniques: intravital magnetic resonance imaging of a camera with AVP, postmortem microcomputed

tomography with MICROFIL injection, immunohistochemical examination and staining of histological sections of the chamber contents [50], scanning electron microscopy [56], preparation of corrosive preparations, and injection of Indian ink [43]. Unfortunately, most of the experimental work was descriptive; in the course of their implementation, the quantitative indicators and reliability of the results obtained were not assessed.

Thus, despite the high cost of components and requirements for technical equipment, the technique of tissue-engineered implants with axial blood supply can become a promising alternative to autotransplantation because of lesser trauma and the lack of restrictions in graft shape and size.

CONCLUSION

Despite the successes achieved in the development of autotransplantation technique of vascularized bone tissues, this direction may be extremely relevant for further research. The technique is of great interest in the field of pediatric orthopedics and traumatology given the anatomical characteristics of children, a wider range of diseases, and the high efficiency of using grafts in areas of growing bone.

Moreover, until now, there is no unified approach and recommendations for the use of this method; thus, it remains a field of creativity and experimentation for practicing doctors. For the same reason, bone autotransplantation on a vascular pedicle is rarely performed and, in most cases, is inaccessible to the bulk of patients, despite the promising nature of its use.

Synthetic tissue-engineered implants with axial blood supply can become a possible alternative to both traditional methods and vascularized bone autografts. This approach can level both several disadvantages of allotransplantation and key disadvantages of autotransplantation, namely, limited material for transplantation. Studies on the reconstruction of bone defects using such tissue-engineered materials have shown the qualitative possibility of using this technique, which allows us to highlight its promising potential in practical medicine, but further active development is still needed.

ADDITIONAL INFORMATION

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