NJSC "Astana Medical University"

ANNOTATION

Doctoral Dissertation Abstract
for the degree of Doctor of Philosophy (PhD)

«Evaluation of the effectiveness of heparin-conjugated fibrin hydrogel in the treatment of localized cartilage defects of the knee joint»

Specialty: 8D10100 – Medicine
Author: Tussipkhan Abdygalyuly Toktarov

Scientific consultants:

Doctor of Medical Sciences

M.T. Abilmazhinov

Candidate of Medical Sciences

E. K. Raimagambetov

Foreign scientific consultant:

Doctor of Medical Sciences,

Professor Dr. Mahmut Nedim Doral

Republic of Kazakhstan
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Relevance

Osteoarthritis is one of the most common chronic degenerative-dystrophic diseases of the musculoskeletal system and represents a significant medical and social problem worldwide. Over recent decades, a steady increase in the incidence of osteoarthritis has been observed, which is associated with increased life expectancy, population aging, rising prevalence of obesity, physical inactivity, as well as increased joint load due to changes in lifestyle and occupational activity [1].

It should be noted that osteoarthritis also occurs in younger individuals. In the age group of 25–49 years, the prevalence of the disease is 2,983.5 cases per 100,000 population. With increasing age, this indicator rises significantly – to 23,237.2 per 100,000 among individuals aged 50–69 years and up to 38,418.9 per 100,000 among persons older than 70 years, which corresponds to the involvement of more than one third of this population [2].

A special place in the structure of osteoarthritis is occupied by knee joint involvement (gonarthrosis), which is one of the most common localizations of the disease. According to epidemiological studies, the prevalence of symptomatic knee osteoarthritis is approximately 16% among the adult population and reaches 22–23% among individuals older than 40 years [2]. The knee joint is subjected to significant biomechanical loads, which, in combination with anatomical features, limb axis disorders, previous injuries, and metabolic factors, makes it particularly vulnerable to degenerative changes of the articular cartilage [3].

Patients with knee osteoarthritis account for approximately one third of all individuals with permanent disability caused by diseases of the musculoskeletal system. Therefore, degenerative-dystrophic diseases of the knee joint, in addition to their medical significance, have a pronounced socio-economic impact and create a substantial burden on healthcare and social support systems worldwide [4–7].

Despite significant progress in the treatment of this pathology, restoration of extensive and deep cartilage defects of the knee joint remains one of the most challenging and unresolved problems of modern traumatology and orthopedics [8, 9].

At the same time, it has been established that the key morphological substrate for the development and progression of gonarthrosis at early stages is represented by local damage to the articular cartilage. In the absence of timely treatment, such lesions tend to increase in size and depth, subsequently leading to diffuse degenerative-dystrophic changes in the joint.

Thus, local damage to articular cartilage, especially when accompanied by involvement of the subchondral bone, should be considered a clinically significant form of pathology requiring the use of modern regenerative and reconstructive approaches.

One of the most typical manifestations of such lesions is osteochondral defects. The absence of blood vessels makes cellular regeneration of cartilage tissue extremely limited. In deep osteochondral injuries communicating with the bone marrow cavity, migration of mesenchymal stem cells (MSCs) from the bone marrow into the defect area occurs, which may serve as a cellular source for regeneration. However, in most cases, if damaged cartilage regenerates, it forms fibrocartilaginous tissue that differs

significantly in architecture, matrix composition, and mechanical properties from native hyaline cartilage [10].

Drug therapy for localized cartilage defects of the knee joint is primarily aimed at reducing pain, decreasing inflammatory reactions, and improving joint function. However, currently available pharmacological agents have no proven disease-modifying effect and do not restore damaged cartilage tissue, which significantly limits their therapeutic role in this pathology [11, 12].

Conservative treatment approaches, including physiotherapy and rehabilitation programs, are considered the first-line treatment for osteochondral defects of the knee joint. Nevertheless, these methods are mainly aimed at reducing pain and improving joint function and cannot restore the damaged cartilage structure. Therefore, surgical and regenerative treatment strategies are becoming increasingly important in the management of structural cartilage damage [4, 8–10].

Currently, various surgical methods are used to treat osteochondral defects aimed at stimulating cartilage regeneration in the damaged area. The most widely used techniques include bone marrow stimulation procedures such as multiple microperforations of the articular surface, abrasive chondroplasty, and mosaic osteochondral transplantation. These techniques are intended to activate reparative processes through the mobilization of mesenchymal cells from the bone marrow and the formation of repair tissue within the defect area.

However, clinical experience and long-term follow-up studies demonstrate that these techniques do not always provide complete and stable restoration of native articular cartilage, since in most cases fibrocartilaginous repair tissue with limited biomechanical properties is formed [13].

In addition to surgical approaches, cell-based technologies using autologous chondrocyte transplantation have been applied in some countries for the treatment of cartilage defects [14, 15]. Although this method may enhance cartilage regeneration, it has several disadvantages, including donor site morbidity during cartilage harvesting, difficulties in obtaining a sufficient number of chondrocytes and their expansion in culture, as well as incomplete tissue restoration [16].

Moreover, the use of cellular technologies alone does not always ensure optimal architecture of the regenerating tissue and long-term stability of the formed cartilage repair tissue. Therefore, in recent years increasing attention has been paid to tissue engineering approaches combining cellular components, biomaterial scaffolds, and biologically active factors, which create more favorable conditions for regeneration of cartilage and subchondral bone tissue.

At present, significant expectations for the regeneration of deep osteochondral defects are associated with tissue engineering technologies aimed at restoring the structural and functional characteristics of damaged joints through the use of stem cells, growth factors, and natural biopolymers or scaffolds [17].

Mesenchymal stem cells are considered a promising cellular component for cartilage tissue engineering. These cells are present in almost all organs and tissues. MSCs are characterized by relatively simple isolation and cultivation procedures, the ability to proliferate for long periods in vitro, and the capacity to differentiate into

various specialized cell types, including chondrocytes and osteoblasts. Furthermore, MSCs possess immunomodulatory properties and actively participate in regeneration of damaged tissues, including articular cartilage [17–20].

Taking these data into account, it becomes evident that existing surgical and cellular methods for the treatment of localized osteochondral defects do not ensure formation of fully functional cartilage and are associated with several technological limitations. Therefore, the development of biocompatible tissue engineering constructs capable of maintaining MSC viability, directing their differentiation, and providing controlled release of regulatory factors of chondrogenesis is of considerable interest.

Objective

To evaluate the clinical and functional effectiveness of a newly developed method for treating localized osteochondral defects of the knee joint using a heparin-conjugated fibrin hydrogel.

Research Objectives

1. To develop a method for implantation of heparin-conjugated fibrin hydrogel in patients with localized osteochondral defects of the knee joint.
2. To evaluate the clinical and functional outcomes of treatment using heparin-conjugated fibrin hydrogel through comparative analysis of treatment results.
3. To perform a comparative analysis of osteochondral defect repair in the study groups based on magnetic resonance imaging findings.

Scientific novelty

A novel method for the treatment of localized osteochondral defects of the knee joint using a heparin-conjugated fibrin hydrogel has been developed (Patent application No. 2025/0656.1, under review).

The comparative study confirmed the clinical and functional effectiveness of heparin-conjugated fibrin hydrogel in the treatment of localized osteochondral defects of the knee joint.

Theses Submitted for Defense

1. The developed method of implantation of heparin-conjugated fibrin hydrogel provides a 2.4-fold greater improvement in WOMAC scores ($p < 0.001$) and a 2.1-fold greater reduction in VAS scores compared with the control group ($p < 0.001$).
2. The application of the developed method promotes restoration of osteochondral defects of the knee joint according to MRI (MOCART) findings: the effect was 1.6 times greater at 6 months and 2.0 times greater at 12 months compared with the control group ($p < 0.001$).

Practical significance

1. The study substantiates the possibility of using the developed implantation technique of heparin-conjugated fibrin hydrogel in clinical practice as an alternative method for treating localized cartilage defects of the knee joint.
2. Implementation of the proposed method expands the possibilities of joint-preserving treatment of localized osteochondral defects and may contribute to slowing the progression of degenerative changes in the joint.

3. Development and production of the heparin-conjugated fibrin hydrogel in the Republic of Kazakhstan will reduce dependence on imported analogues and increase the availability of innovative regenerative treatment methods.

Implementation in practice

An implementation act has been issued for the clinical application of the method: "Implementation of heparin-conjugated fibrin hydrogel for treatment of localized cartilage defects of the knee joint".

Relation of the Dissertation to Other Research Projects

The dissertation work was carried out within the framework of the scientific and technical program of targeted funding of the Ministry of Health of the Republic of Kazakhstan No. OR11465426-OT-22 "Implementation of innovative tissue engineering technologies in medical practice for the restoration of damaged joints".

Author's contribution

The author, together with scientific consultants and the research team, developed the method of implantation of heparin-conjugated fibrin hydrogel for the treatment of osteochondral defects of the knee joint. The author performed patient screening and recruitment at the National Scientific Center of Traumatology and Orthopedics named after Academician N.D. Batpenov and participated in the formation of the study database and clinical treatment of patients during the collection of clinical material.

The author independently performed analysis and statistical processing of clinical, instrumental, and laboratory data of patients with localized osteochondral defects of the knee joint and conducted a literature review on existing treatment methods for this pathology.

All materials were systematized, documented, and presented in the form of the dissertation by the author personally.

Approbation of the Work

The main provisions of the dissertation were presented at the Academic Council of the National Scientific Center of Traumatology and Orthopedics named after academician N.D. Batpenov. The results of the research were discussed at international scientific conferences: "Horizons of Modern Traumatology and Orthopedics" (Turkestan, 2022); Young Scientists Competition "Batpenov Readings" within the IV Congress of Traumatologists-Orthopedists of the Republic of Kazakhstan and III Congress of KATO (Astana, 2024); Young Scientists Competition "Batpenov Readings" within the conference "Modern Approaches in Traumatology, Orthopedics and Rehabilitation: Innovations and Practical Application" (Karaganda, 2025).

Publications

Based on the dissertation materials, 5 scientific papers have been published, including 3 articles in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan and 2 articles in journals indexed in the Scopus database.

Structure and volume of the dissertation

The dissertation consists of 81 pages of typed text and includes an introduction, three chapters, conclusions, and a list of references. The bibliography contains 110 sources. The dissertation includes 34 figures and 8 tables.

No conflict of interest has been declared.

Materials

An open, single-center, prospective, non-randomized controlled study was conducted from May 2022 to December 2023 at the Republican State Enterprise "National Scientific Center of Traumatology and Orthopedics named after Academician N.D. Batpenov" of the Ministry of Health of the Republic of Kazakhstan, Astana, in the Department of Orthopedics No. 5. A total of 80 patients with a verified diagnosis of grade II–III knee osteoarthritis were recruited.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee of the National Scientific Center of Traumatology and Orthopedics named after Academician N.D. Batpenov (Ministry of Health of the Republic of Kazakhstan) on April 29, 2022. All patients included in the study, after receiving detailed information about the study, signed an informed consent form for participation, surgical intervention, and publication of the obtained data without personal identification, with assignment of an individual registration code.

Inclusion criteria:

The inclusion criteria for the study were:

– age from 25 to 65 years, both sexes;

– patients with localized articular cartilage lesions of the knee joint (Outerbridge grade II–IV). Cartilage defect size not exceeding 10 cm^2 for a single defect or 15 cm^2 for multiple defects;

– stable knee joint without significant deformities;

– absence of chronic cardiovascular and neuroendocrine diseases in the exacerbation stage;

– failure of conservative treatment.

Exclusion criteria:

– age under 25 years or over 65 years;

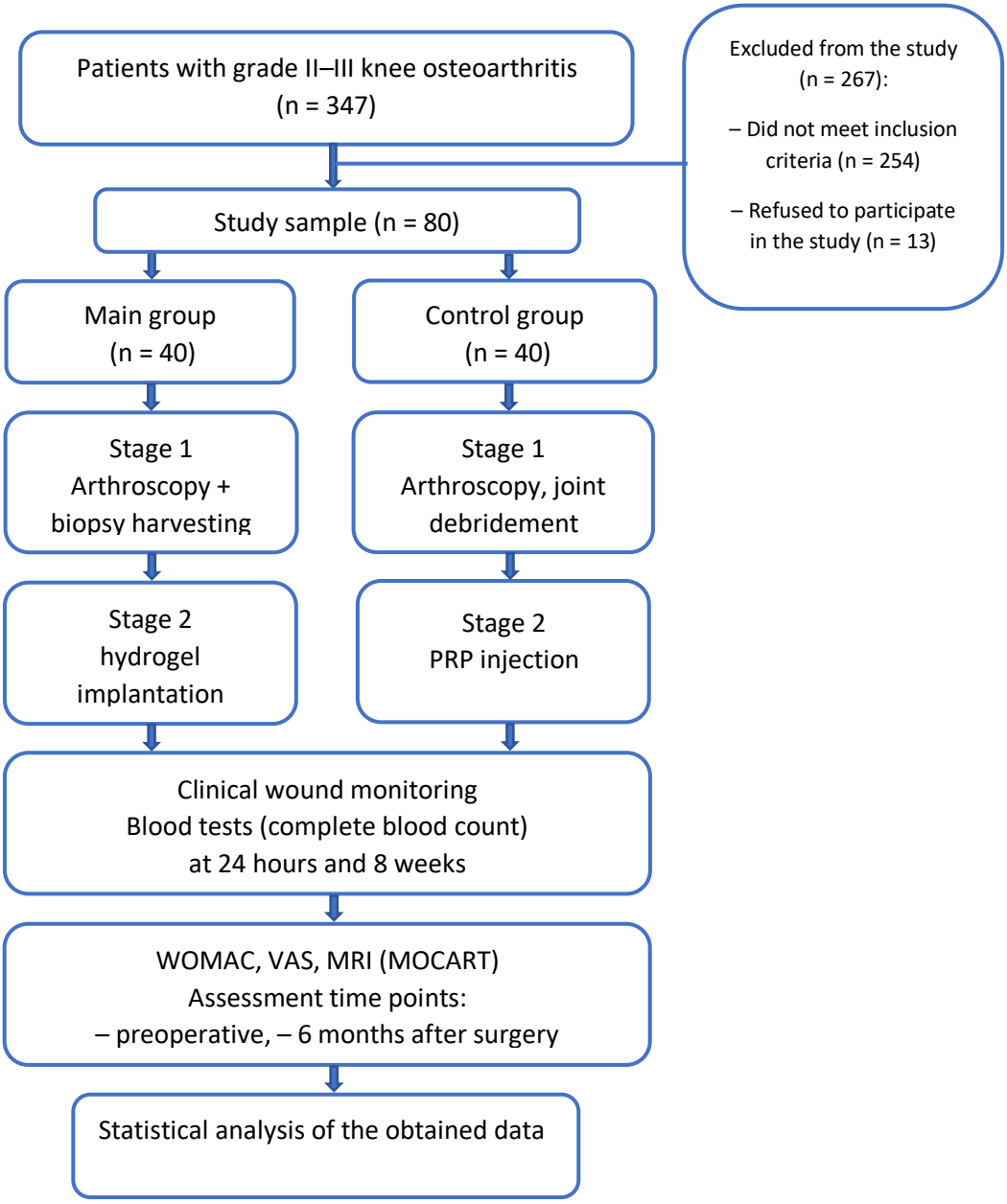
– progressive osteoarthritis (Kellgren–Lawrence grade >3);

– inflammatory arthritis with severe deformity, synovitis, or patellofemoral instability;

– chronic cardiovascular and neuroendocrine diseases in the exacerbation stage;

– refusal to participate in the study.

Study Design



Methods

To evaluate treatment outcomes and perform their comparative analysis, all patients included in the study underwent clinical examination as well as laboratory and instrumental diagnostic methods, including radiography and magnetic resonance imaging (MRI). In addition, validated questionnaires assessing the clinical and functional condition of the studied joints and quality of life were applied.

The following questionnaires (scales) were used in this study:

– Western Ontario and McMaster University Osteoarthritis Index (WOMAC) — a scoring system designed to assess the condition of patients with osteoarthritis, particularly of the knee and hip joints.

– Visual Analog Scale (VAS) — a tool used to measure pain intensity on a scale from 0 to 10.

Clinical and functional assessments of patients were performed prior to treatment and during follow-up at 6 and 12 months after surgery.

Additionally, in order to evaluate the biological compatibility and safety profile of the applied method, dynamic clinical monitoring of the postoperative period was performed to identify potential complications and assess tissue repair processes in the surgical area.

The clinical follow-up protocol included regular assessment of the surgical site and knee joint condition to enable early detection of signs of inflammatory reactions, impaired wound healing, and other postoperative complications.

Clinical monitoring was carried out in the early postoperative period at 24 hours after surgery, which was necessary for the analysis of the acute phase response of the organism to surgical trauma and biomaterial implantation. A repeated examination was performed 8 weeks after surgery, corresponding to the phase of active tissue remodeling, allowing evaluation of the dynamics of reparative processes in the surgical area.

Laboratory evaluation included dynamic assessment of complete blood count (CBC) parameters (erythrocytes, leukocytes, platelets, and erythrocyte sedimentation rate). Venous blood samples were collected before surgery, 24 hours after implantation, and 8 weeks after surgery. This observation protocol made it possible to assess the systemic inflammatory response to surgical intervention and biomaterial implantation, as well as to monitor the dynamics of tissue repair processes.

Conclusions

1. The developed method of surgical treatment of osteochondral defects of the knee joint using heparin-conjugated fibrin hydrogel containing autologous mesenchymal stem cells (MSCs) and growth factors TGF-β1 and BMP-4 enables filling of the osteochondral defect area with a biological matrix and creates favorable conditions for tissue regeneration.

2. The application of the developed method leads to a statistically significant improvement in the functional condition of the knee joint. The WOMAC score in the main group decreased from 52.8 ± 19.3 points to 39.5 ± 12.4 points after 6 months and to 23.5 ± 8.9 points after 12 months, whereas in the control group it changed from 54.0 ± 16.8 to 45.8 ± 15.7 after 6 months and to 41.6 ± 14.9 after 12 months ($p < 0.001$). A reduction in pain intensity according to the VAS scale was also observed. In the main group, pain decreased from 7.0 [5.9–7.0] points before surgery to 5.0 [4.2–5.0] points at 6 months and to 2.0 [1.9–2.5] points at 12 months. In the control group, the VAS score decreased from 6.0 [5.7–6.7] before surgery to 4.6 [4.3–5.0] after 6 months and to 4.0 [3.7–4.3] after 12 months ($p < 0.001$).

3. According to MRI findings, restoration of the osteochondral tissue structure was observed in the main group. The MOCART score in the main group reached 43.5 points (Q1–26.2; Q3–40.7) at 6 months and 60.25 points (Q1–56.2; Q3–64.3) at 12 months after surgery. In contrast, in the control group the MOCART score was 27.5 points (Q1–25.5; Q3–31.5) at 6 months and 30.0 points (Q1–28.2; Q3–33.8) at 12 months ($p < 0.001$), indicating more complete osteochondral tissue regeneration when using the developed technology.

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