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Опыт применения гиалуроната натрия (препарата Ревиск) у пациентов с остеоартритом коленных суставов в клинической практике

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Обоснование. Остеоартрит — заболевание, высоко ассоциированное с широким спектром коморбидных патологий, что приводит к существенным ограничениям возможности его лечения, в частности, постоянному применению нестероидных противовоспалительных препаратов. Актуальна разработка алгоритмов эффективного лечения остеоартрита, направленных на снижение потребности в противовоспалительной терапии.

Цель исследования — оценить эффективность и безопасность препаратов гиалуроновой кислоты для лечения остеоартрита у пациентов с коморбидной патологией.

Материалы и методы. Обследованы 30 пациентов в возрасте от 40 до 65 лет со II–III стадиями остеоартрита по классификации Kellgren – Lawrence, получавших гиалуроновую кислоту. Курс лечения включал в себя стандартные внутрисуставные инъекции в коленные суставы препарата Ревиск (стерильного геля гиалуроната натрия, полученного путем микробной ферментации) 1 раз в неделю, курсом по 3 инъекции. В ходе исследования была разрешена терапия нестероидными противовоспалительными препаратами в стабильных стандартных дозировках. Оценивали эффективность лечения по изменениям индекса WOMAC, боли по визуально-аналоговой шкале в покое и при ходьбе, данных гониометрии, времени ходьбы по прямой на 30 м и по лестнице.

Результаты. Отмечен положительный эффект по всем показателям, а именно достоверное улучшение клинических показателей болевого синдрома по визуально-аналоговой шкале, функциональным тестам и шкалам анкеты WOMAC. Положительная динамика при лечении начиналась с 7-го дня терапии.

Заключение. Препарат Ревиск можно использовать для лечения остеоартрита II–III стадии с умеренно выраженным нарушением функции коленных суставов.

Ключевые слова: остеоартрит; Ревиск; визуально-аналоговая шкала; индекс WOMAC; качество жизни.

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Treatment of patients with knee osteoarthritis with hyaluronate sodium (Revisk) in clinical practice

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BACKGROUND: Osteoarthritis is a disease highly associated with a wide range of comorbidities, which leads to significant limitations of the therapeutic possibilities, in particular, the long-term use of non-steroidal anti-inflammatory drugs. Thus, develop algorithms for effective treatment of osteoarthritis aimed at reducing the need for anti-inflammatory therapy is of great importance.

AIM: To evaluate the efficacy and safety of hyaluronic acid for the treatment of osteoarthritis in patients with comorbid pathology.

MATERIALS AND METHODS: 30 patients aged 40 to 65 years with II–III stages of knee osteoarthritis who received treatment with the hyaluronate sodium were examined according to the Kellgren–Lawrence scale. The course of treatment included standard intra-articular injections of Revisk (sterile sodium hyaluronate gel obtained by microbial fermentation) into the knee joints once a week, in a course of 3 injections. During the study non-steroidal anti-inflammatory drugs therapy was allowed at stable standard dosages. The effectiveness of treatment was assessed by changes in the WOMAC index, the Visual Analog scale pain scores for pain on movement, at rest, goniometry data, 30-meters walking test and stair climb test.

RESULTS: A positive effect of treatment on all the parameters has been noted: significant improvement in clinical indicators of pain according to the visual analog scale, functional tests, and the WOMAC index scores. The positive dynamics of the estimated parameters during treatment started from the 7th day of therapy.

CONCLUSIONS: The hyaluronate sodium (Revisk) can be used for treating patients with II–III stages of knee osteoarthritis with moderate dysfunction of joints.

Keywords: osteoarthritis; Revisk; visual analog scale; WOMAC index; quality of life.

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BACKGROUND

Osteoarthritis (OA, International Classification of Diseases 10th Revision codes M15–M19 "Arthritis") is a joint disease characterized by cellular stress, extracellular matrix degradation due to macro- and micro-damage of cartilage and subchondral bone, abnormal adaptive repair, and immune response.

Changes in the metabolism of joint tissues at the molecular level lead to anatomical and physiological disorders: cartilage degradation, bone remodeling, osteophyte formation, subclinical inflammation, and loss of normal joint function [1].

OA is an organ lesion that involves the cartilage, subchondral bone, synovial membrane, ligaments, capsule, and muscles [2]. It is one of the most common musculoskeletal diseases worldwide. In people aged ≥55 years, this disorder is observed in 10% of cases, and in a quarter of these patients, it has frequent exacerbations and pronounced clinical symptoms [3]. In Russia, 39.5% of the population complains of joint pain, and 26% reported swollen joints. Knee and/or hip joint OA rank first in the nosological structure of these diseases. According to a screening questionnaire, which includes 76,162 adults from 12 regions, the incidence of OA in all Russian citizens aged >18 years is 13% [4].

The main manifestations of OA are mechanical pain, pain at the start of movements, short-term stiffness for up to 30 min, and impaired joint function. The clinical picture may be accompanied by crepitation during active movements, moderate effusion, and bone overgrowth.

OA is associated with an increased risk of death [7], which is explained by low-grade chronic inflammation underlying its pathogenesis, chronic pain syndrome, and high comorbidity rates. Therefore, OA requires careful monitoring and early treatment [5]. The presence of comorbid conditions in patients with OA, among which type 2 diabetes mellitus, coronary heart diseases, and hypertension are the most common, significantly affects OA progression and complicates the choice of therapy for pain management [6].

Because of the high prevalence of OA, therapy, rehabilitation, and social support for such patients have become one of the most important and urgent problems of modern medicine. However, no treatment is universally recognized for this disease. The main goals of OA therapy include pain reduction, preservation or improvement of joint function, prevention of worsening functional insufficiency, improvement of patients' quality of life, and prevention and reduction of adverse events from pharmacotherapy.

Currently, national and international clinical guidelines from organizations such as the Osteoarthritis Research Society [8], European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [9, 10], European League Against Rheumatism [11], and American College of Rheumatology (ACR) [12] often implement different approaches for conservative and surgical treatment of OA.

According to these regulations, conservative treatment should include physical activity modification, weight correction, and use of orthoses, kinesiotaping, nonsteroidal anti-inflammatory drugs (NSAIDs), and symptomatic slow-acting drugs for OA.

The ESCEO conditionally recommended intra-articular glucocorticoid administration in cases of gonarthrosis, whereas the ACR strongly recommends it.

The ACR and ESCEO recommendations differ with regard to intra-articular hyaluronic acid (HA) injections. ESCEO indicates that HA injections can be a good alternative to NSAIDs for knee OA, particularly in older patients. ACR experts believe that the effects of HA injections are identical to those of intra*articular saline injections (placebo effect) [12].

There are pathogenetic bases for the intra-articular administration of HA in patients with knee OA.

HA is synthesized by various cells of the human body and is a part of the extracellular matrix, acting as a natural shock absorber and lubricant, compensating for mechanical stress, and providing glide [13]. HA forms the basis of the synovial fluid and articular cartilage and exerts their interconnection, elasticity, and resistance to stress [14]. Changes in HA structure are associated with their insufficient synthesis because of a decrease in the number and metabolic activity of chondrocytes and rapid destruction due to chronic catabolic inflammation, which is determined by the activation of aggressive enzymes, such as matrix metalloproteinases and hyaluronidases.

HA is an important regulator of anabolic and immune processes because of its association with receptors on chondrocytes, fibroblasts, and macrophage cells. It interacts with several cellular receptors, such as hyaladherin, CD44 (a receptor on the surface of chondrocytes and synovial fibroblasts), toll-like receptors of inflammatory response cells 2 and 4, and adhesion molecules located on the surface of synovial cells [15]. As a result, HA prevents the activation of the interleukin-1b receptor, which indirectly reduces nuclear factor kappa-bi formation and production of tumor necrosis factor-α, interleukins-17 and -6, inducible form of nitric oxide, and cyclooxygenase 2 expression and reduces the activation of proteolytic enzymes ADAMTS4/5 and matrix metalloproteinases 1, 2, 3, 8, 9, and 13 [16, 17].

These events stimulate the synthesis of the structural elements of the protein-polysaccharide complex of the extracellular matrix, slowing of the chemotaxis of immunocompetent cells and reduction of the production of

proinflammatory substances, acceleration of chondrocyte maturation, and suppression of osteoclast differentiation [18]. The HA drugs used differ in the presence of cross-links in their molecules, concentration, viscosity, volume of the administered drug, dosing regimen, and combinations with other active substances [19].

The mechanism of action of HA largely depends on the molecular weight. Thus, the effect of low- and medium-molecular-weight HA drugs is mediated by their interaction with CD44-receptors, stimulation of endogenous high-molecular-weight HA production, and consequently improvement of the mechanical properties of the synovial fluid [20]. As the molecular weight of HA preparations increases, their ability to interact with CD44-receptors decreases, the "sliding" of articular surfaces improves, the concentration of proinflammatory mediators decreases, and the synthesis of proteoglycans improves [21].

The concept of viscosupplementation was the primary explanation of the effect of HA drugs on OA. Once in the joint, HA undergoes biodegradation, and its rate depends on the size of the molecule and presence of chemical "cross-links" between the polymer chains. The half-life period of low-molecular-weight HA is several days (maximum 4 weeks for fully synthetic non-animal stabilized HA); however, the effect of HA does not stop after this period. On the contrary, it grows and lasts for a long time, up to 6–12 months [22]. According to the meta-analysis conducted by Bellamy et al., after a course of HA treatment, pain was reduced by 28%–54%, and joint function improved by 9%–32%. That is, the symptomatic effect of a course of HA therapy is comparable to the long-term use of standard doses of NSAIDs [23]. A series of HA injections reduced pain by 40%–50% on average compared with the initial level [24]. Ten meta-analyses compared the effects of HA and placebo; a positive effect of HA therapy on pain and function was confirmed in 5 and 4 of these studies, respectively. The effectiveness was maintained up to 26 weeks after the course of therapy. The revealed phenomenon confirms the advisability of using this remedy in real practice [25].

Possible positive effects are associated with the effect not only on chondrocytes but also on the synovial membrane, which was confirmed by Pasquali Ronchetti et al. who compared the effect of five weekly intra-articular injections of HA and three injections of methylprednisolone in 99 patients with OA. Arthroscopic biopsy of the synovial membrane was performed 6 months after completing the treatment course and showed a decrease in local inflammation in both groups, and a significant decrease in synoviocyte disorganization and suppression of neoangiogenesis was still observed in the HA group [26].

This study aimed to evaluate the efficacy, tolerability, and safety of intra-articular injection of HA (Revisc) in patients with primary knee OA.

MATERIALS AND METHODS

A non-interventional observational study of 30 patients (26 women and 4 men) aged 45–75 years with a diagnosis of stage II or III knee joint OA was conducted in the rheumatology department of E.E. Eichwald Clinic of North-Western State Medical University named after I.I. Mechnikov in 2022.

The inclusion criteria were as follows: a diagnosis of "primary tibiofemoral OA" confirmed according to the criteria of the ACR [27] in men and women aged 45–70 years, pain on walking of at least 40 mm on the visual analog scale (VAS), radiological stage II or III OA according to the Kellgren–Lawrence classification, need for taking NSAIDs for at least 30 days in the previous 3 months, and signed informed consent to participate in the study.

The exclusion criteria were as follows: diagnosis of "secondary OA," therapy with other symptomatic agents and drugs with the slow development of effect in the last 6 months, intra-articular administration of other drugs 6 weeks before inclusion, and presence of chondrocalcinosis, aseptic necrosis of the femoral and tibia condyles, surgical intervention on the knee joint, history of hypersensitivity to HA, and severe comorbidities, including systemic rheumatic diseases.

The use of NSAIDs in stable dosages at the time of inclusion in the study was allowed. Other intra-articular injections, including glucocorticoids and other NSAIDs, and physical therapy procedures were not allowed.

Examination methods included physical examination, measurement of body mass index, completion of the VAS pain questionnaire, determination of the WOMAC index and Leken functional index, assessment of pain severity at rest and movement by VAS (0–100 mm), stair walking time for 10 steps (in seconds), straight walking time for 30 m (in seconds), general clinical blood test, C-reactive protein measurement, radiography, and magnetic resonance imaging.

Changes in the WOMAC index and its parameters were used as performance indicators: total pain score (when walking on a level surface and when going down/climbing stairs), stiffness, and functional insufficiency. Patients evaluated the need for NSAIDs throughout the study and the overall effect at the end of the study.

Safety indicators such as the frequency and nature of adverse drug reactions and their association with the therapy were studied.

SPSS version 16.0 was used in the statistical analysis of data. The results are presented as mean and standard deviation.

Clinical characteristics of the patients

The study included 26 (86.6%) women and 4 (13.4%) men aged 55.6 ± 5.2 years. The disease duration ranged from 5 months to 14 years (7.8 ± 2.1), and the average

Table. Dynamics of clinical parameters

Таблица. Динамика клинических показателей

Indicator	Day 0	Day 21	Day 90	*t*-criterion	Statistical significance
Visual analog scale of pain on movement, mm	39.6 ± 7.6	34.8 ± 6.9	28.6 ± 5.2	14	$p < 0.01$
Visual analog scale of pain at rest, mm	13.4.8 ± 5.7	7.1 ± 3.5	4 ± 3.2	17.9	$p < 0.01$
WOMAC index, points	42.3 ± 7.8	33.5 ± 3.5	25.8 ± 6.6	27.9	$p < 0.01$
Walking time in a straight line 30 m, s	63.8 ± 7.6	61.5 ± 7.9	57.7 ± 7.9	17.9	$p < 0.01$
Walking time on the stairs, s	23.9 ± 2.1	–	21.8 ± 2.21	15	$p < 0.01$

duration of an exacerbation requiring NSAID use was 3.6 ± 1.65 weeks.

The majority of the patients ($n = 20$, 66.6%) had radiological stage III OA according to the Kellgren–Lawrence classification, and 10 (33.4%) patients had radiological stage II. All patients had bilateral knee joint involvement.

The average body mass index was 29.4 ± 4.1 kg/m^2, 12 (40%) had grade I obesity, 11 (36.6%) had high body mass index, 5 (16.6%) had normal body mass index, and 2 (6.6%) had grade II obesity.

Before the start of treatment, patients complained of pain of mechanical nature (starting pain, during walking, and static load) and limited active and passive movements of the knee joints. The patients took NSAIDs in standard dosages without any significant effect.

The treatment course consisted of three injections of 2 mL of HA (Revisc) solution at weekly intervals into both knee joints. Concomitant NSAID therapy was maintained in doses equivalent at the time of inclusion in the study. Injections were performed by physicians with special training in a room equipped for intra-articular injection of the drug, observing all rules of asepsis. During the procedure, the patients did not experience pain at the injection site, and no knee joint tumescence was observed.

At the end of the procedure, the patients were advised to limit their physical activity for a day.

RESULTS

During the therapy, no adverse reactions were detected. All 30 patients completed the study, indicating a compliance rate of 100%.

In 3 months after the start of Revisk therapy, joint pain syndrome improved in all patients, as shown by the dynamics of the HAS pain index at rest and on movement, WOMAC index in general, pain, stiffness, and functional insufficiency.

The VAS score of pain on movement before therapy decreased from 39.6 ± 7.6 to 28.6 ± 5.2 mm, the VAS score of pain at rest decreased from 13.4.8 ± 5.7 mm to 4 ± 3.2 mm, the pain at rest disappeared in eight patients, which led to NSAID cessation.

The WOMAC index before therapy was 42.3 ± 7.8, and after 3 months of therapy, it was 25.8 ± 6.6, which improved by 16.4 ± 3.2 points.

At the end of treatment, all patients showed significant improvement of joint movements, absence of synovitis, morning stiffness, and pain in the large joints subjected to treatment. The dynamics of the clinical parameters are presented in Table.

A statistically significant decrease in joint pain was detected during Reviscom therapy. Positive dynamics began 1 week after the first injection and reached clinical significance by day 90 of treatment: a decrease in pain on movement by 11 mm and pain at rest by 9.4 mm.

Eight patients (26%) stopped taking NSAIDs completely, and 43% reduced the dose by half or started taking NSAIDs no more than once every 3 days. However, 31% of the patients still need to take NSAIDs (Fig. 1).

During treatment, three patients had arthralgia after the injection, which independently resolved within 2 days after the first injection.

Subsequent injections did not cause an increase in pain syndrome. Based on single blood pressure measurements at follow-up visits, no patients had increased blood pressure

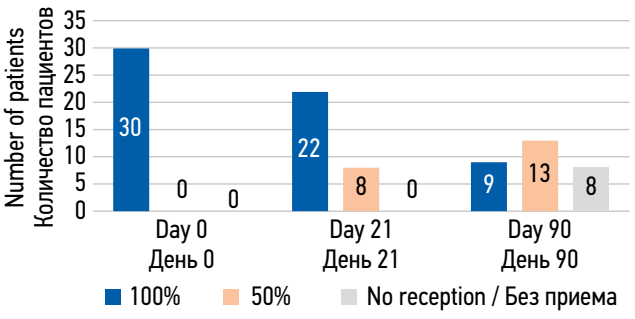

Fig. 1. Dynamics of non-steroidal anti-inflammatory drugs intake

Рис. 1. Динамика приема нестероидных противовоспалительных препаратов

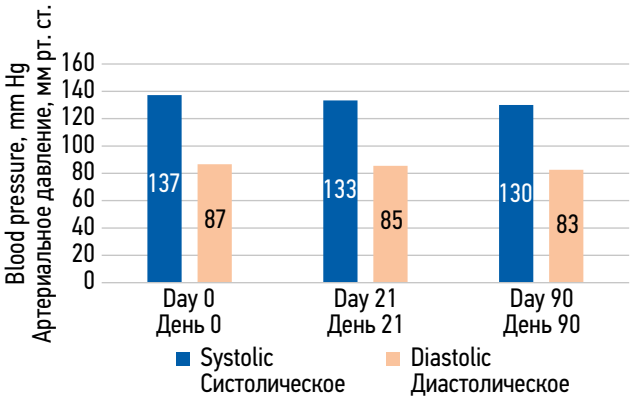

Fig. 2. Dynamics of systolic and diastolic blood pressure based according to the results of single measurements at appointments

Рис. 2. Динамика систолического и диастолического артериального давления по результатам разовых измерений на визитах

during treatment, and patients who discontinued NSAIDs had a decrease in systolic and diastolic blood pressure of 7 ± 3 and 4 ± 1 mm Hg, respectively (Fig. 2).

CONCLUSION

The results of the study of the intra-articular administration of HA Revisc in patients with stage II and III OA showed no significant systemic or local complications, and the presence of arthralgia in three patients was not clinically significant. In general, the tolerability to the drug was good, and statistically significant reductions in VAS scores of pain on movement and at rest and WOMAC index were achieved. Patients had improved functional ability based on the results of the walking test on a level surface and stairs. In addition, eight patients stopped taking NSAIDs, which characterizes well the symptomatic effect of Revisc.

In turn, the reduction in NSAID intake led to a decrease in the risk of complications and comorbidities; in particular, the systolic and diastolic blood pressure decreased in patients who stopped taking NSAIDs.

The clinical effect began to develop on day 21 and continued after drug discontinuation, with maximal changes on day 90 from the start of therapy.

The use of Revisc in patients with OA is pathogenetically sound and safe; moreover, its symptomatic effect is associated with several advantages in the treatment of patients with comorbidities and multimorbidities. Thus, intra-articular injection of Revisc reduces joint pain and stiffness, improves joint function, reduces the daily requirement for NSAIDs, and has high safety, and the effect of therapy is observable within 3 months.

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Author contributions. All the authors confirm the compliance of their authorship with the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

The greatest contribution is distributed as follows: *V.I. Mazurov, M.S. Shostak* — study design; *M.S. Shostak, I.A. Leineman, E.A. Trofimov* — conducting experiments, data analysis, writing the text, literature review.

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