

New biopolymer medical device named Noltrex in combined treatment of gonarthrosis

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Authors describe the successful use of a new medical device named Noltrex in the treatment of 60 patients with knee osteoarthritis.

Key words: arthrosis, arcoxia, gonarthrosis, noltrex, diprospan.

Gonarthrosis (OA), caused by a disturbance in the function of synthesis chondrocytes, together with the destruction of cartilage and the subchondral bone, significantly worsens the patients' quality of life and presents a serious socioeconomic problem, being one of the main causes of long-term loss of productivity and patient disability. Every second person on this planet aged over 55 years suffers from knee osteoarthritis to a varying degree [6, 12]. At the same time, the pathological process is not only limited to the hyaline cartilage, but is also present in the synovial membrane, the subchondral bone, the joint capsule, the intra-articular ligaments and the periarticular muscles. Together this leads to the development of recurring synovitis, degeneration and destruction of the cartilage, bony remodelling, joint capsule sclerosis, meniscal degeneration, and periarticular muscle atrophy [2, 3, 7]. Physiotherapy intervention is only effective at the early stages of knee osteoarthritis, together with chondroprotectors.

Traditionally, fast acting drugs are used in the treatment of knee osteoarthritis (analgesics, NSAIDs, corticosteroids, preparations containing hyaluronic acid such as Fermatron, etc) and disease-modifying agents (glucosamine sulfate, chondroitin sulfate, etc) [4, 5, 9].

Non-steroidal anti-inflammatory drugs are the preferred choice (such as Butadion, Indomethacin, Piroxicam, Diclofenac, Ketoprofen, Ibuprofen, etc), since combined therapy for gonarthrosis is ineffective without them. The positive effect of NSAIDs on knee osteoarthritis is not only due to their anti-inflammatory effect, but also their significant pain relieving properties [9, 12-14]. This decrease in pain is linked to a suppression of cyclooxygenase-2 (COX-2), a key enzyme in the synthesis of anti-inflammatory prostaglandins. All the researchers point to the need to prescribe NSAIDs as early as possible once knee osteoarthritis symptoms appear.

To reduce the gastrointestinal adverse effects caused by NSAIDs, it is helpful to use COX-2 selective NSAIDs. If symptoms such as indigestion, gastric or duodenal ulcers or erosion appear, Omez (omeprazole), Almagel, Gastal, Maalox,

and such, are prescribed. Of some interest is Arcoxia (Merck & Co, USA), which has recently appeared on the Russian pharmaceutical market. Arcoxia (etoricoxib) is one of the coxibs, a selective inhibitor of COX-2. According to studies, the frequency of perforations and hemorrhage in the upper gastrointestinal tract was 55% lower as compared to traditional NSAIDs. The drug also has a long analgesic effect (one 60 mg tablet is required per day).

Local glucocorticoid therapy plays an important role in the treatment of knee osteoarthritis. The use of glucocorticoids in the treatment of knee osteoarthritis leads to a fast and effective suppression of the aseptic inflammatory process in the synovial membrane, bursa, tendon sheath and entheses, controlling synovitis after just one application. Glucocorticoids are divided into two groups according to the method of action: short-acting and long-acting.

Short-acting glucocorticoid drugs include hydrocortisone and prednisolone, and can be administered into the soft tissues (including intramuscularly). Long-acting glucocorticoids are usually administered into the large joints.

We prefer Diprospan – a long-acting aqueous suspension of Betamethasone, which contains two active ingredients: 1) 2 mg of highly soluble, fast-acting ester of betamethasone disodium phosphate; and 2) 5 mg of the poorly soluble, slow-acting and slowly absorbable fraction of betamethasone dipropionate.

The advantage of Diprospan is the presence of its two fractions, which start to act 2-4 hours after administration, and then continue to have an effect for up to 4-6 weeks due to the presence of the slow-acting fraction. The potency of Diprospan is 25 times higher than hydrocortisone. Moreover, Diprospan is safer to use due to a lower frequency of administration and more financially advantageous for patients with limited financial means. Also, Diprospan crystals have a rounded shape, which reduces the risk of mechanical and chemical irritation, with an ensuing reactive synovitis due to synovial damage caused by the sharp edges of the crystals. These features of Diprospan also allow it to be

painlessly administered into the peri-articular tissues. Doctors have ascertained that Diprosan does not cause local dystrophic changes in the tissues.

Hyaluronic acid agents such as Fermatron, Ostenil, Synvisc, Orthovisc, Hyalgan, and Arthrum are also administered intra-articularly [1, 10, 11]. These drugs are widely used, but they have a short duration of action, as well as allergic and even infectious complications after their intra-articular administration.

The largest pharmaceutical companies in many countries, including Russia, have been busy for a long time creating a more effective synthetic polymer to replace joint synovial fluid, which would have high viscosity, an anti-bacterial effect, biocompatibility, and slow resorption rates, for the treatment of patients with knee osteoarthritis.

In this article we present our experience of using Noltrex, a new Russian-made medical product for synovial fluid replacement, developed at CJSC "Research center "Bioform" in collaboration with clinicians at the M. F. Vladimirovskiy Moscow Regional Scientific Research Clinical Institute, and research laboratory staff at the I.M. Sechenov First Moscow State Medical University. Thanks to the unique properties (including thixotropic) and the matrix structure of the polymer Noltrex, its treatment effect is significantly greater and it is therefore already in use in many European countries for the treatment of patients with osteoarthritis. Noltrex is a synthetic polymer material containing no animal products or any ingredients of animal origin, and is not a natural metabolite. Noltrex is composed of a 3-dimensional polyacrylamide, purified water and silver ions. Noltrex is a viscous and gel-like substance with a color that varies from clear to light yellow, has a unique formula, which ensures a high degree of biocompatibility with human tissues and bactericidal properties due to the presence of the silver ions.

Materials and methods

Sixty patients participated in the study (12 men and 48 women), aged 55 to 85 years. We conducted a comprehensive clinical study over 9 months to assess the effectiveness of the polymer Noltrex, its tolerability and duration of after effect in patients with knee osteoarthritis. Patients were divided into 2 groups, with 30 people in each.

Patient inclusion criteria for the study were: knee osteoarthritis confirmed on X-ray in accordance with the ACR criteria (clinical classification of arthritis accepted by the American College of Rheumatology).

Patients in group I received Noltrex, manufactured at the CJSC "Research center "Bioform" (Russia), which was injected into the knee joint once a week (2.5 ml) over 5 weeks, with 5 injections in total. In addition, the patients received 7.5 mg of the non-steroidal anti-inflammatory drug Movalis twice a day for 10 days. Patients in group II only received 7.5 mg of Movalis twice a day for 10 days. The assessment was done at the beginning of the study (before the first injection) and then 1, 3, 6 and 9 months after the treatment began.

The mean age of patients in group I was 63.8 ± 4.7 years, and in group II it was 62.4 ± 5.2 years. Disease duration was 7.4 ± 3.2

years and 6.9 ± 3.1 years respectively. The majority of patients had stage III knee osteoarthritis. Group I had three patients with verified stage II gonarthrosis, and 27 patients with stage III gonarthrosis. Group II had four patients with stage II knee osteoarthritis and 26 with stage III. The control and treatment groups were compared by gender, age, duration and stage of disease.

Study results

Prior to the start of the injection therapy, pain severity in the knee joint at rest was compared in group I and group II patients, and was 38.4 ± 4.2 and 36.1 ± 4.7 mm respectively on the VAS (Visual Analogue Scale). The statistical significance level was greater than 0.05 ($p > 0.05$).

As a result of the treatment undertaken, patients with knee osteoarthritis had a significantly reduced level of pain with the positive effect accumulating over time. At the same time, by 9th month patients in group II experienced an increase in pain at rest up to 26.7 ± 3.0 on the VAS, while the level of pain experienced by patients in group I was not significantly different (12.3 ± 2.4), ($p < 0.01$) (Pic. 1).

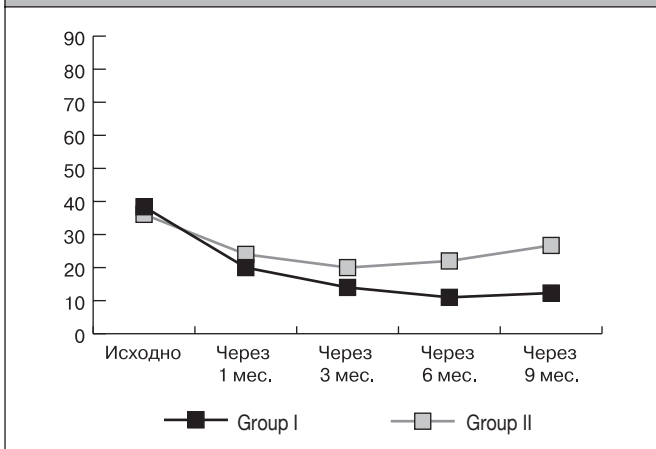
Pic.1 shows that the level of pain during movement, as measured by the visual analogue scale, was nearly twice the level of rest in the two patient groups, which is a pathognomonic symptom of knee osteoarthritis.

The mean value on the VAS was 78.4 ± 5.3 in group I and 75.9 ± 5.7 in group II. A decrease in pain during movement was noted with the administered therapy, and it was more pronounced in patients in group I, who received the combined therapy (Noltrex + Movalis). Thus, only three months after treatment there was a significant difference in pain severity between the study groups (35.3 ± 4.5 versus 48.9 ± 6.2 mm according to the VAS, $p < 0.01$). At the end of the study these values were 34.7 ± 4.5 and 55.6 ± 6.4 mm respectively ($p < 0.01$) (Pic. 2).

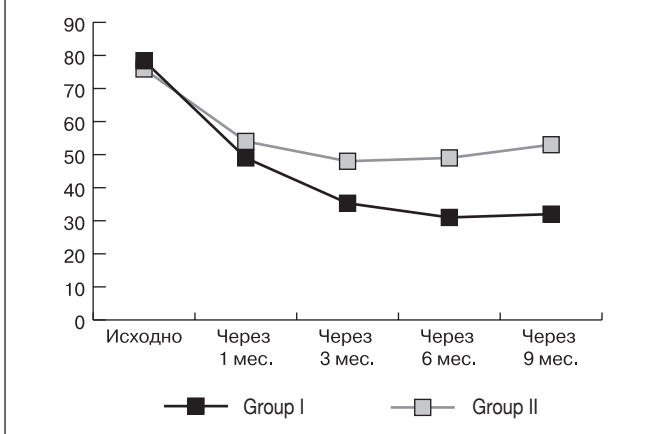
We also assessed the patients in both groups using the international WOMAC index (Western Ontario and McMaster University Arthritis Index), which evaluates effectiveness and course of osteoarthritis treatment and consists of 24 parameters. There was a significant reduction in the WOMAC values as a result of the treatment and this difference was more pronounced in group I. The initial levels in groups I and II were 778 ± 56.3 and 760 ± 61.4 respectively. After one month, the values decreased to 623 ± 45.8 and 684 ± 54.3 , while after three months, the values were 532 ± 39.7 and 650 ± 64.3 respectively. Six months after treatment, the WOMAC index level continued to drop in group I (441 ± 48.4), while the trend was not as pronounced in group II (645 ± 58.2). Nine months after treatment an increase in WOMAC values was noted and it was more pronounced in group II (453 ± 51.8 and 683 ± 59.8 respectively) (Pic. 3 and 4).

The evaluations of treatment effectiveness by both patient and doctor were nearly the same. A significant improvement was noted by the doctor in 13 cases (43.3%) and by the patient in 14 cases (46.7%) in group I, while in group II a significant improvement was noted by the doctor in 10 cases (33.3%) and by the patient in 8 cases (26.7%). No effect was noted in one

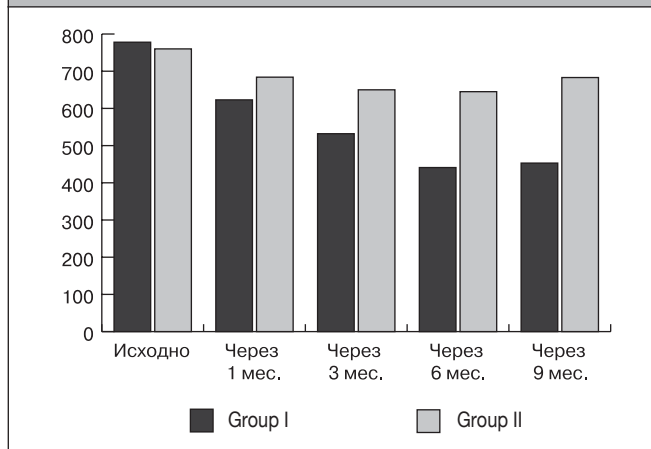
Pic. 1. Dynamics of pain at rest according to the visual analogue scale



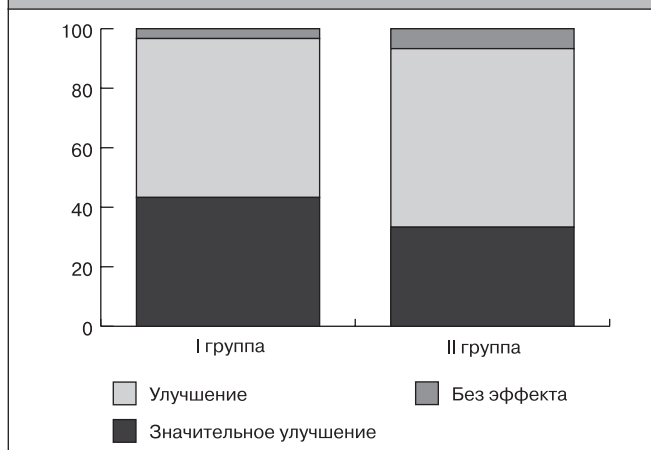
Pic. 2. Dynamics in pain during walking according to the visual analogue scale



Pic. 3. Changes in the WOMAC index in the study groups



Pic. 4. Rating of treatment effectiveness according to doctor



case by the doctor and patient (3.3%) in group I, and in three cases by the doctor (10%) and in two cases by the patient (6.7%) in group II. There was no worsening of the condition noted in any of the patients (Pic. 4 and 5).

Intra-articular administration of Noltrex was well tolerated by patients with gonarthrosis in both groups. Only two patients (6.7%) in group I and three patients (10%) in group II reported epigastric pain, which was due to NSAID use and was not related the effects of Noltrex.

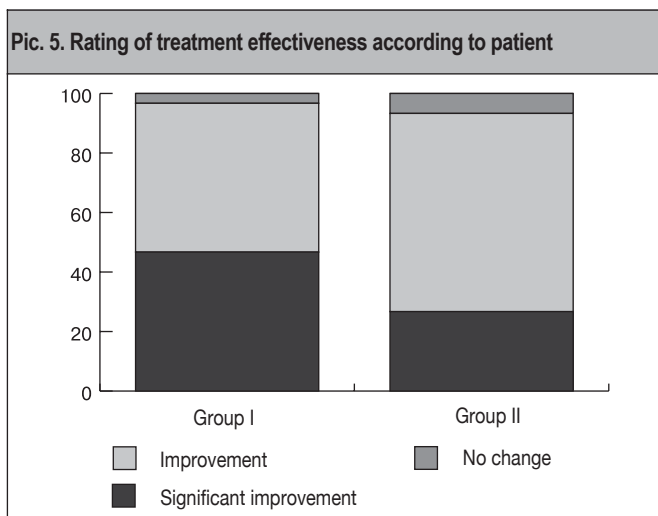
Discussion

The treatment effect of Noltrex after the very first injection into the knee joint in patients with gonarthrosis was related to the regeneration of viscoelastic properties of the synovial fluid, a normalization of the endogenous proteoglycan synthesis by chondrocytes, and a retardation or inhibition of the destructive process in the cartilage. The patients experienced a significant treatment effect regardless of the stage and duration of knee osteoarthritis.

Noltrex is a 100% synthetic synovial fluid implant (prosthesis). Due to the presence of silver ions in the compound it has intra-articular bactericidal properties and improves the biological functions of the synovial capsule.

Noltrex also has analgesic, anti-inflammatory, antioxidant and chondroprotective properties. We did not administer Noltrex in the presence of clinical symptoms of acute synovitis, as well as increased ESR and C-reactive protein in the laboratory tests. We also did not use Noltrex in children and pregnant women. At the present time, Noltrex is approved for use in all countries of the European Union, the CIS (Ukraine, Kazakhstan, Armenia, Georgia) and other countries (Turkey, Colombia, etc.).

On the basis of a combined study we came to the conclusion that Noltrex, as a gel endoprosthesis for the knee joint, assists in reducing the contact between opposing joint surfaces, easing the symptoms of osteoarthritis quickly and for a long time. This is achieved by creating favorable biological and biomechanical conditions in the internal environment of the knee joint and this demonstrates that Noltrex is highly effective and safe for the treatment of patients with any stage of gonarthrosis. Thus we predict a more widespread use of Noltrex in the research and clinical setting by arthrology and orthopedic specialists, as well as rheumatologists.



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