STUDY OF EFFICACY AND SAFETY OF DIART® IN THE TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS OF THE II-III GRADE

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Application in clinical practice of new class of drugs – symptom modifying slow-action drugs (SMOADs) – has significantly broadened treatment and rehabilitation measures in patients with knee osteoarthritis. Here belong drugs based on chondroitin, glucosamine and hyaluronic acid. These drugs are characterized by slower effect as compared to symptomatic drugs, however, this effect lasts after one stops taking them.

Hyaluronate was discovered by Karl Meyer in 1934 while he worked at the ophthalmological clinic at the Columbian University. He isolated this substance from a cow's vitreous body under acid conditions and called it hyaluronic acid from Greek word hyalos — meaning vitreous and uronic acid that was one of the components of this polymer. During the following ten years Karl Meyer and some other authors isolated hyaluronate from various tissues. For instance, it was found in joint fluid, umbilical cord and tissue of cock's comb. The chemical structure of the polysaccharide molecule was deciphered by Karl Meyer and his colleagues in the 1950s. Hyaluronate is a long polymeric molecule that consists of disaccharide parts which components are N-acetyl-D-glucosamine and D-glucuronic acid, interconnected by B1-4 and B1-3 connections.

In 1972 Hardingham and Muir showed that hyaluronate can bind to proteoglycans of cartilaginous tissue. Researches done by Hascall and Heinegard found that hyaluronate can be specifically bound to N-terminal domain of proteoglycans' globular part and connective proteins. This link is quite strong and onto one chain of hyaluronate there can be several proteoglycans which result in formation of large molecular aggregations in the cartilage and other tissues. In 1979 Underhill and Toole showed that hyaluronate binds to cells and 1985 saw isolation of the receptor responsible for this interaction. In 1989 2 groups of authors simultaneously published their works where they showed that lymphocyte homing receptor CD44 can link to hyaluronate in the cartilaginous tissue. Another hyaluronate-binding protein isolated later from the supernatant of 3T3 cell culture in 1982 by Turley and co-authors was RHAMM (receptor for hyaluronate mediating motility). At the beginning of the 1970s Bryan Toole and Jerome Gross showed that during regeneration of a new limb in frog larva hyaluronate was synthesized at the very beginning and then due to hyaluronidase its amount decreases with hyaluronate being replaced by chondroitin sulphate. This research was fundamental for the modern hyaluronic acid-based drugs.

Application of drugs based on hyaluronic acid has become a pioneer direction in osteoarthritis treatment. In osteoarthritis concentration and molecular mass of hyaluronic acid in synovial fluid is reduced which causes decrease of its viscoelastic properties. Injection of exogenic hyaluronic acid into a joint restores the joints and normalizes cushioning and lubricating properties of synovial fluid.

Therefore, scientists and clinicists are particularly interested in studying hyaluronic acid efficacy in reducing pain syndrome and improving functional conditions of joints. Hyaluronic acid-based drugs fall into 2 main groups: high- and low-molecular. It is recognized that therapeutic effectiveness of high- molecular compounds is higher. Randomized controlled comparative 12 week study of the effectiveness of hyaluronic acid high- and low-molecular compounds showed that effect of high- molecular compounds regarding pain management is significantly higher (Wobia M. et al., 1999). Till February 2002 there were published the results of 39 clinical trials of hyaluronic acid in knee osteoarthritis: from 20 placebo-controlled studies 18 showed evident advantage of hyaluronic acid. However, improvement of patients' conditions with hyaluronic therapy can be achieved during longer period of time as compared to symptomatic treatment that is related to slower beginning of the effect.

Despite the fact that nowadays there are a lot of publications on hyaluronic acid properties and its place in medical practice, still there are few clinical trials proving its symptom-modifying effect.

Our trial studied effectiveness of intra-articular injection of fixed-dose hyaluronic acid combination (hyaluronate concentration 1.8%) and sodium succinate under the trade name "Diart". Presence of sodium succinate in the drug stipulates the possibility to influence main pathogenetic osteoarthritis links. Sodium succinate has expressed antihypoxic action which is explained by the influence on mediator amino acids transport, stimulates synthesis of cell regenerative equivalents (system of succinic acid oxidation misses slow stages of Krebs cycle and enables to significantly accelerate energy-generation processes), reduces concentration of lactate, pyruvate and citrate accumulating in the cells during early stages of hypoxia, and also enhances compensatory activation of aerobic glycolysis and reduces degree of depression of oxidation processes in mitochondria.

Aim of the paper. To study effectiveness, tolerance and safety of Diart in the treatment of patients with knee osteoarthritis of the II and III grade.

Object of research. In the clinics of SE «Gerontology Institute of the Academy of Medical Sciences of Ukraine» 20 patients aged 50-75 with the primary knee osteoarthritis of the II and III grade according to Kellgren-Lawrence were examined with the help of approved clinical and radiological diagnostics methods. The trial accepted women with pain syndrome on VAS 4-6 cm and more with primary knee osteoarthritis. At the moment of inclusion all the patients were under out-patient observation in the International Osteoarthritis Centre, but did not receive at that moment or during the previous 4 weeks any drug or non-drug means of osteoarthritis treatment. The research did not include the patients with secondary knee osteoarthritis, hypersensitivity to any component of the drugs under research, as well as with any skin damages in the knee joint area. Depending on the treatment scheme the patients were divided into the following groups:

I group – main group, 10 patients taking Diart once per 7 days (3 injections), or 21 days (average age 61.8±6.5 years);

II group — comparative group, 10 patients taking daily diclofenac sodium 50 mg dose twice per 24 hours during 21 days (average age 63.2±7.4 years).

After finishing treatment all the patients were observed during 2 months to study the after-effect.

Methodology of the research. The research applied clinical, instrumental and orthopaedic and neurological examinations to diagnose primary knee osteoarthritis. X-ray of knee joints was conducted to determine the grade of osteoarthritis according to Kellgren-Lawrence. Ultrasound of knee joint was done to produce differential diagnostics and evaluation of knee soft tissues condition. Evaluation of severity and dynamics of pain syndrome in knee joints was done with the help of self-report method by means of McGill Pain Questionnaire (Huchkinson, Melzack), 11-component Visual Analogue Scale (VAS/BAIII), pain level was daily evaluated by a patient individually and was fixed in pain diary. Algo-functional status of patients was evaluated by means of WOMAC questionnaire. Functional condition of knee joints was determined by means of functional tests — 15-meter and 6-minute tests. Patients' quality of life was evaluated with EuroQol–5D (1) questionnaire, while changing of this indicator in the course of treatment — with EuroQol–5D (2). Tolerance evaluation and side effects control were done during each visit. Adverse events and side effects of the therapy were fixed. Patients were examined before the course of treatment, after the treatment (after 21 days), after 1 and 2 months from the beginning of the treatment course.

Findings of the Research. Studies of pain syndrome peculiarities data from McGill Pain Questionnaire showed that emotional characteristic of pain in knee joints which is characterized by descriptor and rank index, after the course of treatment (21 days) and during observation period (1 and 2 months) in both groups under research has been changing in a similar way. However, it was found out that the patients of the I group showed significant decrease of the descriptor index after 2 months of observation (before the treatment 11.0±6.1 and in 2 months 7.8±5.4; t=2.61. p=0.05; Fig. 1 A). At the same time the I group showed significant decrease of pain index after treatment (before the treatment 5.2±0.9 and in 21 days 4.2±1.4; 1=1.94, p=0.05; Fig. 1 C), though the differences between the groups were not significant.

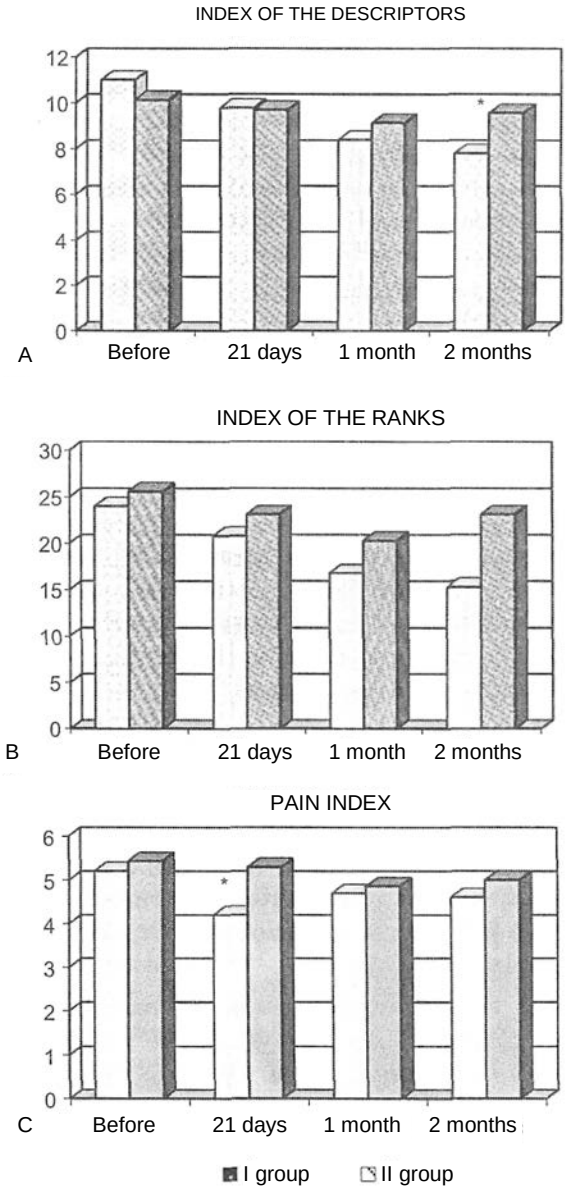

Fig. 1. Change of indicators of McGill Pain Questionnaire during Diart treatment and observation period: A – index of the descriptors, B – index of ranks, C — pain index, * – p<0.05 significant changes in respect of initial indicator.

The dynamics of indicator decrease in respect of initial one was 6.1% in the I group and in the II — 0.2% after 21 days of treatment, after 1 month of observation 16.5% and 8.3%, after 2 months - 25.4% and 2.7% respectively. Rank index decreased in the I group by 4.7% and in the II — by 10.7% after 21 days of treatment, after 1 month of observation by 16.8% and 29.3%, after 2 months — 25.8% and 2.7% respectively. Pain index after 21 days of treatment decreased in the I group by 17% and in the II — by 2.4%, after 1 month of observation by 4.7% and 4.9%, after 2 months – 8.8% and 8.3% respectively. There was no significant difference in the decrease of indicators between the groups.

Knee joints are the largest joints in the skeleton carrying the greatest weight-bearing load, therefore, pain syndrome in knee osteoarthritis is very multilateral and can manifest itself with different degree (intensity) both under condition of rest and under the condition of physical load. The results of studying peculiarities of changes of pain syndrome intensity under different static and dynamic conditions in the course of the treatment enabled to establish significant differences both in the indicators before the treatment within each group and also between the groups (Table 1).

Thus, at the moment of reporting the level of pain (VAS-1) after the treatment significantly decreased in both groups (I group - t=4.12; p=0.003; II group - t=2.83; p=0.03). However, during the observation period significant decrease of this type of pain in knee joints was observed only in the I group (after 1 month - t=2.38; p=0.04, after 2 months - t=2.75; p=0.02). Typical or average level of pain (VAS-2) significantly decreased in the I groups during the observation period (after 1 month - t=2.18; p=0.05, after 2 months — t=2.37; p=0.04), while the control group only showed tendency towards decrease of this indicator.

Table 1. Dynamics of pain syndrome intensity in the course of treatment as based on the data of 11-component VAS, points (M±SD).

Period of treatment / Pain characteristics	Before the treatment	21 day	1 month	2 months
I group				
Pain at the moment of reporting	5.00±1.25	3.60±1.84*	4.10±1.29*	3.40±1.43* #
Typical or average level of pain	5.50 + 1.43	4.90±0.74	4.40+1.43	4.50±1.08*
Pain level in the best periods of the disease	3.50 + 1.18	2.80+1.32*	3.60±1.26	2.90±1.45
Pain level in the worst periods of the disease	7.80+1.40	6.60 + 1.65*	6.60±1.43*	6.30+1.89*
Starting pain	4.40±1.90	4.30+1.70	3.70+1.49	4.00+2.31
Pain during long walks	6.90+1.20	6.10±1.60	6.30±1.16	5.40±1.43*
Pain during long rest	3.70 + 1.34	2.50 + 1.43* #	3.10±1.20	2.70*1.49
Constant incessant pains	4.20±1.69	3.20±1.55* #	3.30±1.42*	2.60*1.78* #
Pain while walking upstairs	5.90+2.64	4.90+2.38	4.60+1.90	4.40+2.37*
Pain while walking downstairs	5.70+2.00	5.60+2.46	4.80±1.99	5.00±2.05
Pain while walking on even surface	4.80±0.79	3.80±1.69* #	4.10±1.66	4.10+1.52
II group				
Pain at the moment of reporting	5.86±1.77	5.29±2.06*	5.29+2.14	5.43±2.57
Typical or average level of pain	6.14+1.68	5.71 + 1.60	5.29+1.60	5.00±1.83
Pain level in the best periods of the disease	4.71+2.14	4.14+1.95	3.57 + 1.90	4.14+2.48
Pain level in the worst periods of the disease	8.14+1.21	7.71 + 1.38	6.86+1.21	6.86+1.86
Starting pain	5.57±1.72	5.14±1.68	4.86±1.77	4.86±2.41
Pain during long walks	7.29±2.69	6.71±2.43	6.57+2.51	6.29±2.50
Pain during long rest	4.71 + 1.80	4.71 + 1.98	3.86 + 1.35	3.86±2.12
Constant incessant pains	5.14+1.57	5.29+2.21	4.29+2.14	4.71±2.50
Pain while walking upstairs	5.86+1.35	6.29±1.70	5.86±1.35	6.00±2.45
Pain while walking downstairs	7.00±1.83	6.43+3.05	6.14+3.13	6.00±3.11
Pain while walking on even surface	6.14+1.35	6.00+2.38	5.14+2.19	5.29+2.56

N o t e s : * - $p<0.05$ significant differences as compared to the indicators before the treatment in each group; # - $p<0.05$ significant differences as compared between the groups.

The I group after the course of treatment showed significant decrease of the level of pain in the best periods of the disease (minimal level of pain, VAS-3), which was not observed in the II group, despite this there was no significant change of this indicator in both groups during the observation period. However, the level of pain in the worst periods of the disease (maximum level of pain, VAS-4) and constant incessant pains (VAS-8) significantly changed in the I group after the course of treatment (t=2.34; p=0.04 and t=2.74; p=0.02 respectively), and remained after 1 (t=2.17; p=0.05 and t=2.86; p=0.02 respectively) and 2 (t=2.29; p=0.05 и t=2.95; p=0.02 respectively) months of observation. In the II group there was no significant change in the level of maximum pain. In the course of the treatment none of the groups showed significant changes in the level of starting pain (VAS-5) and pains while walking downstairs (VAS-10). Level of pains during long walks (VAS-6) and pains while walking upstairs (VAS-9) significantly decreased only after 2 months of observation in the I group (t=3.14; p=0.01 and t=3.74; p=0.005 respectively), while pain during long rest (VAS-7) and walk on even surface (VAS-11) – in the same group after treatment course (t=2.88; p=0.02 and t=2.24; p=0.05 respectively). The control group did not show significant changes in the level of the pains mentioned.

Despite positive results of the conducted treatment in the I group as compared with the indicators before the treatment, comparison with the II group showed significant differences only in terms of the pain level at the moment of reporting after 2 months of observation (F=3.24; p=0.05), level of pain during long-lasting rest after the course of treatment (F=l,9; p=0.02), constant incessant pains – after the course of treatment (F=2.04; p=0.04) and after 2 months of observation (F=l.98; p=0.05), as well as pains during walks on even surface after the end of treatment (F=l.99, p=0.04).

According to the international Womac scale, studies on the dynamics of algo-functional condition of patients with knee osteoarthritis revealed significant changes in the I group. Thus, according to the pain syndrome subscale (Womac 1-5) there is significant decrease of pain intensity in knee joints after 21 days of treatment (t=2.64; p=0.03), after 1 (t=2.96; p=0.02) and 2 (t=3.13; p=0.02) months of observation (Fig. 2 A). The results of comparison of therapy efficacy between the groups showed significantly larger decrease of Womac 1-5 indicator in the I group both after the course of treatment (F=2.27; p=0.01) and during the observation period (1 month - F=l.15; p=0.01 and 2 months F=2.11; p=0.05). Indicator dynamics was 25.6% after 21 days in the main group, in the control group — (-12.7%), after 1 month - 25.6% and 6.1%, after 2 months -29,0% and 13.2% respectively in the I and II groups (Fig. 2 B).

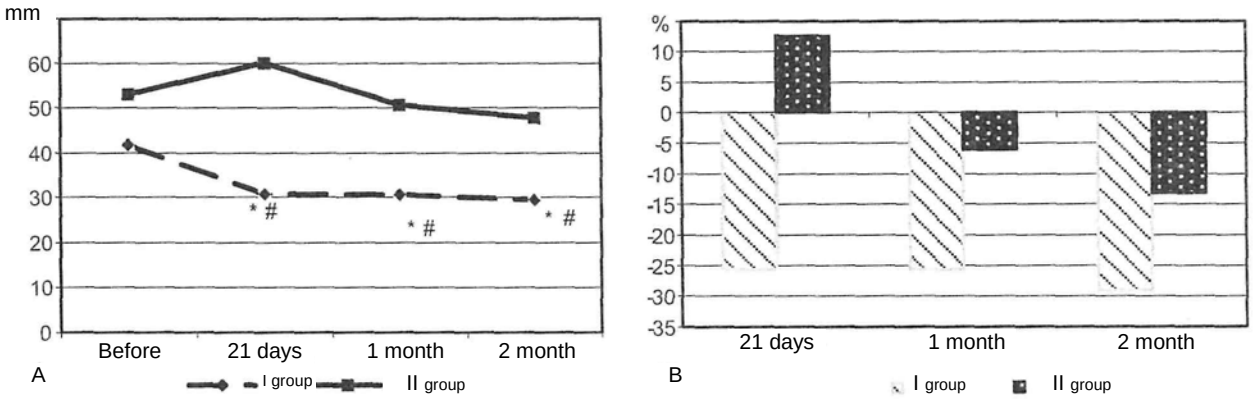

Fig. 2. Dynamics of indicators of pain subscale (Womac 1-5) in the course of the treatment and during the observation period: A – in points to the initial indicator; B - in % initial indicator; * - significant changes s compared to the indicator before the treatment, p<0.05; # - p<0.05 significant differences as compared between the groups.

The results of the analysis of stiffness subscale dynamics (Womac 6-7) did not reveal significant changes of the indicator in both groups both immediately after the therapy and after 1 and 2 months of observation, in the I there was only the tendency (Fig. 3 A). The results of therapy efficacy comparison between the groups showed significantly larger decrease of the indicator Womac 6-7 in the I group after the course of treatment (F=l,47; p=0.03) and after 1 month of observation (F=l,78; p=0.04). Indicator dynamics constituted 8.1% after 21 days in the main group, in the control group - (-10.2)%, after 1 month - 18.2% and (-0.3)%, after 2 months - 14.9% and 6.6% in the I and II groups respectively (Fig. 3 B).

The results of changes of everyday activity subscale (Womac 8-24) showed significant improvement in the conditions of patients, taking Diart, after the therapy course (t=2.58; p=0.03), after 1 (t=2.64; p=0.03) and 2 (t=3.15; p=0.01) months of observation (Fig. 4 A). Despite the positive dynamics of the indicator Womac 8-24, there were no significant differences in the therapy efficacy between the groups. There was only tendency towards more evident indicator decrease in the I group as compared to the II group after 21 days (F=l.29; p=0.08) and after 1 month (F=l,22; p=0.06). The indicator dynamics was 17.6%, after 21 days in the main group, in the control group - (-0.6)%, after 1 month — 21.8% and 3.9%, after 2 months — 23.8% and 12.6% in the I and II group respectively (Fig. 4 B).

The results of studying the dynamics of the functional tests in the course of the treatment and during the observation period made it possible to establish peculiarities of therapy impact onto patients' physical abilities, in particular, distance walk and time walk.

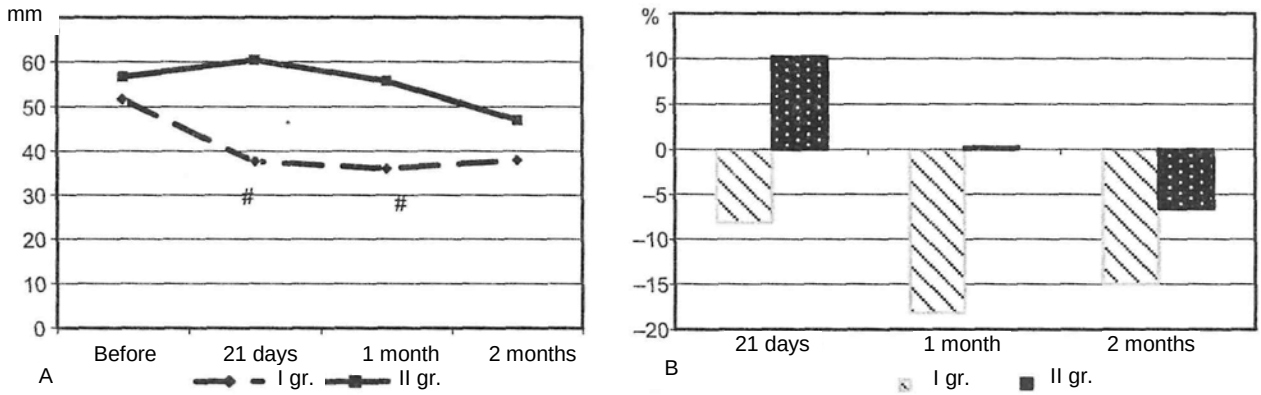

Fig. 3. Dynamics of stiffness subscale indicators (Womac 6-7) in the course of the treatment and during observation period: A – in points to the initial indicator; B - in % to the initial indicator; # -p<0.05 significant differences as compared between the groups.

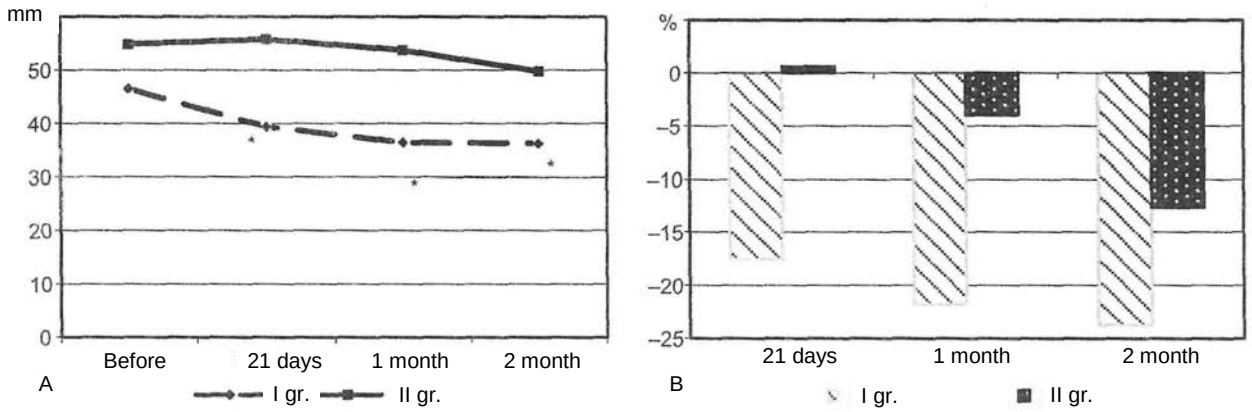

Fig. 4. Dynamics of everyday activity subscale indicators (Womac 8-24) in the course of the treatment and during observation period: A - in points to the initial indicator; B - in % to the initial indicator; * - significant differences as compared to the indicator before the treatment, p<0.05.

Thus, the results of the 15-meter test (time for which the patient covers 15-meter distance walking with average speed) did not reveal significant changes of the indicator during the research in the control group, while in the main group there was significant decrease of time necessary to cover 15-meter distance both immediately after the treatment (t=6.11; p<0.0001) and during observation period 1 (t=l,18; p=0.01) and 2 (t=2.68; p<0.001) months (Fig. 5). The results of the comparative analysis between the groups showed significantly better indicators in the main group after 1 (F=l.18; p=0.01) and 2 (F=2.68; p<0.001) months of observation.

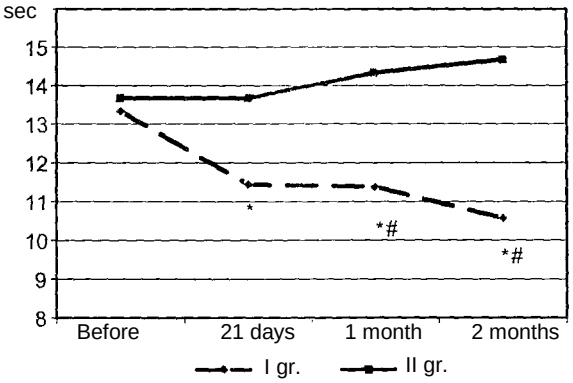

Fig. 5. Dynamics of the results of the 15-meter test in the course of the treatment and during observation period; * - significant changes as compared with the indicator before the treatment, p<0.05; # — p<0.05 significant differences as compared between the groups.

Analysis of the results of the 6-minute walk test (distance, covered by the patient for 6 minutes of walk at a usual pace) showed significant improvement of the indicator in both groups after the course of treatment (I gr. - t=5.3; p=0.001 and II gr. - t=4.62; p=0.04). However, during the observation period the positive effect significantly remained only in the I group (1 month - t=4.62; p=0.04 and 2 months - t=4.62; p=0.04) (Fig. 6). The results of the comparative analysis between the groups showed significantly better indicators in the patients of the main group both after the course of treatment (F=2.22; p=0.05) and during observation period after 1 (F=5.86; p=0.01) and 2 (F=6.98; p=0.05) months.

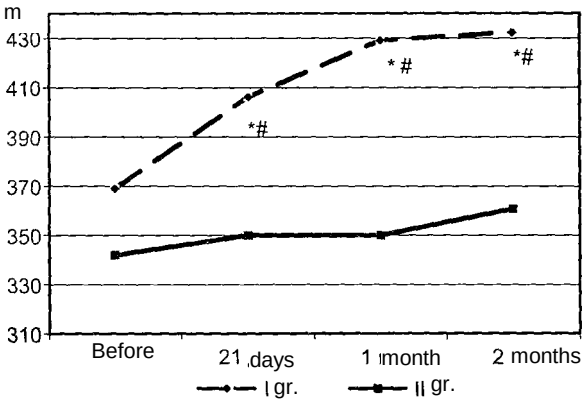

Fig. 6. Dynamics of the results of the 6-minute walk test in the course of the treatment and during observation period: * - significant changes as compared with the indicator before the treatment, p<0.05; # - significant differences as compared between the groups, p<0.05.

According to the questionnaire EuroQol-5D(1), the treatment resulted in the significant improvement of patients' quality of life in the I group after the course of treatment (from 5.2±0.63 to 4.6±0.97, t=2.6; p=0.05), after 1 (to 4.5±1.3, t=2.9; p=0.05) and 2 (to 4.2±1.7, t=2.3; p=0.05) months. The II group showed only tendency towards improvement of this indicator during the whole clinical trial. The results of therapy influence onto the patients' quality of life (EuroQol–5D (2)) showed significant improvement in both groups after 1 month of observation (I gr. — from 1.0±0.47 to 0.3±0.48, t=2.6; p=0.03; II gr. - from 0.86+0.38 to 0.29±0.49, t=2.8; p=0.03). There were no significant differences between the groups regarding quality of life indicators and therapy influence onto the quality of life of the patients with knee osteoarthritis.

Conclusions. Thus, application of the Diart in the patients with knee osteoarthritis of old age groups positively influences the course of the disease: there is evident decrease of pain syndrome and improvement of functional condition. Influence of Diart on algo-functional status of the patients outperforms the effect of traditional NSAID therapy.

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