DIART IN THE PATHOGENETIC TREATMENT OF OSTEOARTHRITIS

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Summary. Experiental study on 32 animals allowed to demonstrate and evaluate the severity of the antioxidant effect of a combination of hyaluronate and succinate compared with monotherapies hyaluronate. Clinical efficacy of a combination of hyaluronate and succinate in the product Diart in the treatment of patients with osteoarthritis of the knee joint was detected in 126 patients. Was found significant improvement in treatment results in the aspect of security, stability and the resulting prolongation of clinical benefit.

Key words: osteoarthritis, hyaluronate, succinate, treatment

DIART В КОМПЛЕКСНОМ ПАТОГЕНЕТИЧЕСКИ ОБОСНОВАННОМ ЛЕЧЕНИИ БОЛЬНЫХ ОСТЕОАРТРОЗОМ

О. А. Бурьянов, Т. Н. Омельченно, Ю. Л. Соболевский

Резюме. Результаты экспериментального исследования на 32 животных позволили доказать и оценить выраженность антиоксидантного влияния комбинации гиалуроната и сукцината по сравнению с монопрепаратом гиалуроната. Определена клиническая эффективность применения комбинации гиалуроната и сукцината (Diart) в комплексном лечении 126 больных остеоартрозом коленного сустава. Установлено достоверное улучшение результатов лечения больных в аспекте безопасности, пролонгации и стойкости полученного клинического эффекта.

Ключевые слова: *остеоартроз, гиалуронат, сукцинат, лечение.*

DIART В КОМПЛЕКСНОМУ ПАТОГЕНЕТИЧНО ОБГРУНТОВАНОМУ ЛІКУВАННІ ХВОРИХ НА ОСТЕОАРТРОЗ

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Резюме. Результати експериментального дослідження на 32 тваринах дали змогу довести та оцінити вираженість антиоксидантного впливу комбінації гіалуронату і сукцинату в порівнянні з монопрепаратом гіалуронату. Визначена клінічна ефективність застосування комбінації гіалуронату і сукцинату (Diart) в комплексному лікуванні 126 хворих на остеоартроз. Встановлено достовірне покращання результатів лікування хворих в аспекті безпеки, пролонгації та стійкості отриманого клінічного ефекту.

Ключові слова: *остеоартроз, гіалуронат, сукцинат, лікування.*

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INTRODUCTION

The issue of searching new methods and pharmacological products for treatment of patients with osteoarthritis is important today due to the fact that the disease embraces almost 80% in the total joint pathology in individuals older than 60 years, 10-30% of cases of osteoarthritis leads to varying degrees of disability. Despite significant advances in the diagnostics and treatment of osteoarthritis, many aspects of its pathogenesis are not fully explored, for which reason medication is often limited to symptomatic pharmacological agents that are not able to provide a stable remission. It was reported that in the last 30-40 years an osteoarthritis incidence increased by 5-9 times. Demographic parameters in Europe and USA confirm continuing "aging" of the population and increase in proportion of people over 60 years. According to preliminary estimates, the population of this age group will double in 2020 [5].

Today the drugs based on hyaluronic acid are widely used for the osteoarthritis treatment. Hyaluronic acid (HA) being a linear polysaccharide belonging to a group of glycosaminoglycans constitutes a repetition of disaccharide units made of N-Acetylglucosamine and glucuronic acid. The combination of 2.5 thousand disaccharide forms HA molecules with a molecular weight of about 5.0 million Da. In this form the HA molecule is available in the intercellular matrix of connective tissue. Especially high HA concentrations is contained in such tissues as skin, cartilage, umbilical cord, synovial fluid, vitreous body.

Hyaluronic acid normalizes viscoelastic, shock absorbing and lubricating properties of synovial fluid, affects intermediate layer nociceptors of synovial membrane and reduces the induction of pain mediators, ensuring pain relieving effect and constituting the basis for aggrecan which is important for the structural and functional integrity of articular cartilage;

retains water molecules to provide the necessary physical properties of synovial fluid, has a protective effect as regards of cartilage cells - chondrocytes, facilitates the penetration of nutrients that are necessary for cartilage matrix building. It is shown that it interacts with specific receptors of cells (CD-44, RHAMM, I-CAM) and reduces the concentration of inflammatory mediators in the synovial fluid, thus enhancing the anti-inflammatory effect, as well as inhibits the activity of enzymes that destroy joint cartilage. Exogenous HA stimulates the synthesis of endogenous HA and synthesis of extracellular matrix components of cartilage, inhibits the loss of cartilage proteoglycans, reduces the level of chondrocytes apoptosis.

It is shown that the decrease in viscoelastic properties of synovial fluid in osteoarthritis increases the sensitivity of cartilage to injury. The results of clinical studies, carried out over the past 20 years, prove high efficiency of HA in patients with osteoarthritis [2-5, 9]. Data from these authors suggest that the synthesis of endogenous HA is activated by exogenous HA. However, the authors point out that without affecting other osteoarthritis pathogenesis chains, especially the processes of accumulating reactive oxygen in localized and integrated environments, the endogenous HA synthesis activation has no lasting character.

Despite the fact that many researchers point out the presence of significant disturbances in the body's antioxidant defence system within the genesis and progression of osteoarthritis, almost none of them complemented the complex treatment with drugs that would have been able to correct these violations, and only in some publications we discovered drugs with metabolic and antioxidant action within medication regimens [1, 5, 19, 22].

Understanding of recent osteoarthritis development mechanisms has become more profound, especially due to studying the viscoelastic properties of synovial fluid and participation of enzymes in the destruction of articular cartilage. In addition, currently more and more information is available on the importance of free radical lipid peroxidation (FRLP) in the pathogenesis of OA and normal functioning of articular cartilage.

The above data revealed potential chondroprotective effects of HA in osteoarthritis, which is associated with inhibition of anabolic and activation of catabolic processes in cartilage. Recently we have witnessed an increasing number of publications dedicated to necessity of using drugs with antioxidant action within the complex treatment of OA.

Summarizing the abovementioned, we clearly understand the need of creating drugs for the treatment of osteoarthritis, the action of which directed at several pathogenesis chains of the disease under consideration.

The first drug of similar action, represented at the domestic market, is Diart. It is a combined preparation of high-molecular, highly purified HA, received by means of biotechnological processing, combined with sodium succinate in a unique formula. Mechanism of action after intra-articular introduction in osteoarthritis involves restoring synovial joint balance and activation of metabolic processes in cells of the articular cartilage by sodium succinate. Sodium succinate provides normalization of intracellular metabolism and cellular respiration under hypoxic conditions by restoring NAD+ through the reverse electron transfer within the respiratory chain of mitochondria, adds to the biotransformation of endoplasmic reticulum xenobiotics, normalizes the physiological state and a range of acid-alkaline balance in acidosis due to changes in hydrogen ions outside the mitochondria, participates in the regulation of K^+ and Ca^{2+} transport, stabilizes the antioxidant and pro-oxidant balance [8].

Studying the influence of drug Diart on the metabolism of cartilage tissue, as well as its antioxidant properties in osteoarthritis resulted in our experimental and clinical research.

The aim was to experimentally prove and examine the clinical efficiency of a hyaluronate and sodium succinate combination in Diart preparation used for treating and preventing the osteoarthritis progression.

OBGECT AND METHODS OF RESEARCH

The experimental study of 32 animals (Chinchilla rabbits) stipulated osteoarthritis modelling through transchondral surgical damage, diameter 2 mm, depth 3 mm, in the area of patellar surface of the right femur. This method of osteoarthritis modelling in animals has been previously tested and used [1, 2, 9, 10]. Subsequently 6 series of experiments were performed to prevent development of dystrophic and degenerative process in the joint and carry out treatment of degenerative process after its development in comparison with placebo and non-stabilized hyaluronic acid. For this purpose the intra-articular injection of 1% hyaluronate solution was used in combination with sodium succinate in the direction of medullary canal at a dose of 0.2 ml 1 time every 7 days, No. 5. Evaluation of results was carried out by means of morphological studies of cartilage from the surgically untreated area and regenerate from the defect areas of the operated joint at the end of the study [4]. Severity of degenerative-dystrophic process in the knee joint was assessed pursuant to the quality and prevalence of symptoms of pathological changes in the structure of articular cartilage. The modified rating scale, provided in the guidelines of experimental studies and anti-arthroses drugs clinical study, approved by the Pharmacological Committee of the Ministry of Health of Ukraine, and the rating scale proposed by the S. W. O'Driscoll et al [11] and S. R. Frenkel et al. [9] constituted the basis of the assessment method.

Functional status of the FRLP system was studied by the blood plasma values. For this purpose the method for detecting spontaneous and Fe2 +-induced super-weak luminescence (chemiluminescence) with the help of chemiluminometer HLMSCH-01 was used [3, 6, 7].

Examination and treatment of 126 patients with osteoarthritis of the knee joint stage I-II pursuant to Kelhrenom and Lawrence, whose average age was (54.3 + 2.7) years was carried out in clinic. There were 75 female (60%) and 51 (40%) male patients. 2 groups of patients with identical pathological process as regards of nature, sex and age were formed. The basic scheme of medical treatment, applicable to 58 patients of the main group, included:

- solution of sodium succinate stabilized hyaluronic acid - Diart - 2 ml intra-articular once a week for 3 weeks;
- Selective as regards of cyclooxygenase-2 nonsteroidal anti-inflammatory agent;
- concomitant medication product chondroprotector;

Patients of the comparison group received an identical scheme of medical treatment using solution of hyaluronic acid without succinic acid pursuant to the identical scheme.

Clinical observation and assessment of treatment outcomes were conducted in dynamics: before the treatment, 6 weeks after the treatment (1.5 months), and to assess the stability of the clinical effect 12 weeks after the treatment (3 months).

Apart from conventional laboratory and instrumental methods of examination the criteria and parameters recommended by EULAR were used while assessing treatment outcome:

determination of the constraint duration and evaluation of everyday activity pursuant to the WOMAC index;

- Assessment of pain pursuant to visual analogue scale (VAS);
- evaluation of the functional state of the knee joint by scoring with a Lisholma scale;
- assessment of patient activity pursuant to the Tehner scale;
- overall assessment of the treatment outcomes by the patient, the overall assessment of treatment outcome by the doctor.

WOMAC index (Western Ontario and McMaster Universities osteoarthritis Index) belongs to the generic methods for assessing the health of patients with osteoarthritis. The test is presented in the form of a questionnaire, including 24 questions that describe pain (5 questions), stiffness (2 questions) and functional ability (17 questions) in patients with osteoarthritis of the knee and hip joints [N. Bellamy et al, 1998]. WOMAC index is considered to be a highly informative indicator, used to assess the efficiency of both pharmacological and non-pharmacological treatment.

Scoring scale, used to assess the functional status of the knee joint pursuant to Lysholm approach (the Lysholm knee scoring scale), which is shown in Table 1, was proposed by Lysholm and Gillquist in 1982 [5]. It is designed to be filled by the patient with the doctor's participation. In 1985 the most recent version of the scale was published, which is currently used. Within the process of general scoring the result is classified as "unsatisfactory", "poor", "good" or "excellent." Absolutely healthy knee joint parameter corresponds to 100 points. Amount equalling to 84 points is considered to be the lower limit of good evaluation result.

Tegner activity Level scale, which is shown in Table 2, was proposed in 1985 [5]. This scale is presented in the form of questions, exploring 11 levels of the patient's possible activity. The patient is offered to choose the level of activity that is consistent with his\her capabilities at the time of inspection. The level 0 corresponds to the maximum disorder, and level 10 represents a fully functional knee joint.

The Visual Analog Pain Rating Scale (VAS) of Huskisson (Visual analog pain scale) is a common tool, used for assessing the pain in many pathological conditions [5]. It is a horizontal line with markings from 0 to 100 mm; its beginning corresponds to the absence of pain and its ending to the maximum pain. To answer the question on the extent of their pain the patient is offered to determine a point on the scale.

RESULTS AND DISCUSSION

Results of morfo-histological study. Osseocartilaginous defect of the patellar surface of the femur epiphysis within 45 and 90 days after injury is filled predominantly by the regenerated fibrous component, cartilage cells turn to small cells in a fibrous cartilage. Articular cartilage of the defect edges is subject to expressed and widespread degenerative and necrotic processes, corresponding the morphological picture of post-traumatic osteoarthritis. The use 1% HA solution in combination with sodium succinate promotes more active formation of cartilage regenerate in defect if compared to the use of 1% solution HA mono-drug.

Table 1

Scale for clinical evaluation of the knee joint functional status (J. Lysholm, 1985)

Indicator	Number of points	Indicator	Number of points
Claudication		Instability with every step	0
No	5	Swelling of the joint	
Periodic or negligible	3	No	10
Significant or permanent	0	Occurs after considerable physical exercise	6
Support ability		Occurs due to everyday stress	2
Complete	5	Is always there	0
Gimp stick or crutches	3	Pain	
The load is not possible	0	No	25
Ascending the ladder		Sometimes after considerable physical exercise	20
No problem	10	Often at great physical exercise	15
Slightly difficult	6	After a long walk	10
Possible step by step	2	After walking less than 2 km	5
Impossible or possible with considerable effort	0	Constant	0
Ability to completely sit		Blockade of joint	
No problem	5	No	15
Slightly difficult	4	Pseudo-blockade "linkage "	10
Maybe up to 90°	2	Rarely	6
Cannot	0	Often	2
Instability		Blocking at the time of examination	0
There is no evident instability	25	**INTERPRETATION Of POINTS**	
Occasionally instability in athletic or other considerable physical exercise	20	unsatisfactorily	0-64
Often instability in athletic or other considerable physical exercise	15	satisfactorily	65-83
Instability sometimes during normal activity	10	good	84-94
Instability often during daily routine activity	5	perfectly	95-100

Table 2

Tegner Activity Level Scale, 1985

Please indicate in the spaces below the HIGHEST level of activity that you participated in BEFORE YOUR INJURY and the highest level you are able to participate in CURRENTLY	
BEFORE INJURY: Level_____ CURRENT: Level_____	
Level 10	Competitive sports- soccer, football, rugby (national elite)
Level 9	Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball
Level 8	Competitive sports- racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing
Level 7	Competitive sports- tennis, running, motorcars speedway, handball. Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running
Level 6	Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week
Level 5	Work- heavy labour (construction, etc.). Competitive sports- cycling, cross-country skiing, Recreational sports- jogging on uneven ground at least twice weekly
Level 4	Work- moderately heavy labour (e.g. truck driving, etc.)
Level 3	Work- light labour (nursing, etc.)
Level 2	Work- light labour. Walking on uneven ground possible, but impossible to back pack or hike
Level 1	Sick leave or disability pension because of knee problems

This allows us assuming that the combination of HA solution of sodium succinate optimize the differentiation of skeletogenous cells into chondrocytes and assists integration of the regenerated cartilage.

In both animals groups within 45 days after transchondral damage the process of reparative regeneration and filling of the articular cartilage defect was accompanied by the development of degenerative and dystrophic changes, embracing the emerging regenerate, as well as articular cartilage beyond the defect area. Expression of these pathological changes in the articular cartilage, which is characteristic of the initial stage of post-traumatic deforming osteoarthritis, was lower in animals, injected with HA solution in combination with sodium succinate after transchondral defect.

Results of studying the changes in free radical lipid peroxidation activity and antioxidant defence mechanism of the organism. In the plasma of the rabbits with experimentally reproduced experimental post-traumatic osteoarthritis of the knee joint there was a typical for dynamic development of the pathological process activation of free radical lipid peroxidation detected, supported by significant increase in spontaneous chemiluminescence level of biological substrate, and under the conditions of peroxidation process initiation by ions Fe2 + - by acceleration of lipid oxidation, accumulation of peroxidation products of free radical reactions and significant increase in resistance to lipid oxidation (Table 4). This being the case the latency period of chemiluminescence slow flash development reduced subsequent to initiation, testifying the presence of antioxidant deficiency. In general, these data indicated the violation of lipid composition of blood plasma in rabbits as a result of previous prolonged activation of the free radical lipid peroxidation activity and development of easily oxidized lipid fractions as a result of the above described deficit.

The prophylactic use of drugs in rabbits at an early stage of experimental post-traumatic osteoarthritis of the knee joint revealed only partial normalization of free radical lipid peroxidation activity in the plasma. The level of spontaneous chemiluminescence (SHL) in the group administered Diart amounted to (640 + 77) counts per minute, while the comparison group scored (684 + 42) counts per minute. In animals not undergoing surgery this figure was within the normal range, which is (442 +55) counts per minute. Indicators of Fe2 +-induced chemiluminescence were characterized by the similar ratio in the two groups of comparison and showed the advantage of an integrated hyaluronate based drug with succinate, used to normalize the body's antioxidant defence system in experimental post-traumatic osteoarthritis of the knee joint prior to using the non-stabilized monohyaluronate (Table 3).

The group of rabbits with experimental post-traumatic osteoarthritis of the knee, which were intra-articularly administered Diart, revealed a clear tendency to decrease in plasma radical lipid peroxidation intensity and enhancing of the latent period duration of initiation reaction of spontaneous chemiluminescence slow flash if compared to control animals. In addition, the rabbits of this group revealed increase it lipid resistance towards peroxidation (Table 4).

At the same time, if compared to rabbits of experimental post-traumatic osteoarthritis of the knee joint group, the drug Diart normalized elevated spontaneous chemiluminescence plasma level and under the conditions of peroxidation process initiation by ions Fe2+ the drug managed to normalize the rate of lipid peroxidation and contents of peroxidation products resulting from free radical reactions. However, the use of the abovementioned drug had no effect on the reduced intensity of the lipid peroxidation process and increased resistance of plasma lipids prior to the peroxidation process. The group of rabbits, which prior to treatment of experimental post-traumatic osteoarthritis of the knee were intra-articularly administered mono-drugs of non-stabilized 1% HA, revealed no changes in the spontaneous chemiluminescence level (Table 4). Under the conditions of initiating in the blood plasma of peroxidation process initiation by ions Fe2+ the reduction in primary radical lipid peroxidation products - lipid hydroperoxides, as well as tendency to growth in peroxidation products contents of free radical reactions and lengthening of the latent period of spontaneous chemiluminescence slow flash.

Table 3

Influence of prophylactic use of drugs in rabbits with experimental post-traumatic osteoarthritis of the knee on the activity of free radical lipid peroxidation in plasma (M ± m)

Series of experiments	Spontaneous chemiluminescence, counts per minute	Fe^{2+}- induced chemiluminescence							
		H, counts per second	H, counts per second	I6, counts per second	<a	t1, c	t2, c	S1, counts per 6 minutes	S2, counts per 6 minutes
1. Control	442 ± 55	38,0 ± 2,1	14,7 ± 1,4	14,7 ± 1,4	3,8 ± 0,2	93,3 ± 0,9	360,0 ± 0,0	3558 ± 599	2430 ± 264
2. Operated	685 ± 176	40,0 ± 2,1	14,0 ± 1,4	14,0 ± 1,4	4,8 ± 0,5	68,7 ± 5,3	360,0 ± 0,0	5702 ± 958	1592±116
3. Experimental (Diart)	640 ± 77	33,6 ± 1,7	12,0 ± 0,8	12,0 ± 0,8	2,8 ± 0,2	67,0 ± 3,2	360,0 ± 0,0	5440 ± 449	1600 ± 457
4. Comparison (1 % hyaluronate)	684 ± 42	35,2 ± 1,7	13,6 ±0,8	13,6 ± 0,8	3,0 ± 0,2	80,0 ± 3,2	360,0 ± 0,0	6241 ± 624	2403 ± 276
p1-2	<0,05	>0,5	>0,5	>0,5	<0,1	< 0,01	>0,5	<0,1	<0,02
p1-3	<0,1	<0,2	<0,2	<0,2	< 0,01	< 0,001	>0,5	<0,05	<0,2
p1-4	>0,5	>0,5	>0,5	>0,5	<0,02	< 0,01	>0,5	<0,02	>0,5
p2-3	>0,5	<0,05	>0,5	>0,5	< 0,01	>0,5	>0,5	>0,5	>0,5
p2-4	< 0,01	<0,2	>0,5	>0,5	< 0,001	<0,2	>0,5	>0,5	<0,05
p3-4	<0,02	>0,5	<0,2	<0,2	>0,5	<0,02	>0,5	> ,5	<0,2

Table 4

Influence of therapeutic use of drugs in rabbits with experimental post-traumatic osteoarthritis of the knee on the activity of free radical lipid peroxidation in plasma (M ± m)

Set of experiments	Spontaneous chemiluminescence, counts per minute	Fe^{2+}- induced chemiluminescence							
		H, counts per second	H, imp/c	H, counts per second	<a	H, counts per second	t2, c	H, counts per second	S2, imp /6 min
1. Control	442 ± 55	38,0 ± 2,1	14,7 ± 1,4	14,7 ± 1,4	3,8 ± 0,2	93,3 ± 0,9	360,0 ± 0,0	3558 ±599	2430 ±264
2. Operated	685 ± 176	40,0 ± 2,1	14,0 ± 1,4	14,0 ± 1,4	4,8 ± 0,5	68,7 ± 5,3	360,0 ± 0,0	5702 ±958	1592 ±116
3. Experimental (Diart)	507 ±3	36,8 ± 4,3	11,2 ±0,8	11,2 ±0,8	3,6 ± 0,4	128,0 ± 2,1	360,0 ± 0,0	3485 ±236	442 ±349
4. Comparison (1 % hyaluronate)	413 ± 63	29,6 ± 0,8	12,8 ±2,6	12,8 ± 2,6	3,2 ± 0,8	117,0 ± 3,2	360,0 ± 0,0	4661 ± 93	2180 ±239
p1-2	<0,05	>0,5	>0,5	>0,5	<0,1	< 0,01	>0,5	<0,1	<0,02
p1-3	>0,5	>0,5	<0,1	<0,1	>0,5	< 0,001	>0,5	>0,5	< 0,001
p1-4	>0,5	< 0,01	>0,5	>0,5	>0,5	< 0,001	>0,5	<0,1	>0,5
p2-3	<0,05	>0,5	<0,1	<0,1	<0,05	< 0,001	>0,5	<0,05	< 0,001
p2-4	<0,02	< 0,001	>0,5	>0,5	<0,1	< 0,001	>0,5	>0,5	<0,05
p3-4	<0,2	<0,2	>0,5	>0,5	>0,5	<0,02	>0,5	< 0,01	< 0,001

At the same time, its use did not change the intensity of the lipid peroxidation process, plasma lipid resistance to overoxidation, normalized increased speed of lipid peroxidation and significantly prolonged the latent period of initiating the spontaneous chemiluminescence slow flash.

Thus, the results of the study confirmed the presence of earlier violations in the free radical lipid peroxidation activity in the blood plasma of rabbits with experimental post-traumatic osteoarthritis of the knee, witnessing the violation of its lipid composition due to prolonged preliminary activation of the free radical lipid peroxidation activity and deficit in easily peroxidized lipid fractions. It was proven, that the use of complex comprising hyaluronate and sodium succinate in Diart if compared to equivalent concentration of 1% of hyaluronate mono-drugs provides a significantly better result in terms of normalization of antioxidant and pro-oxidant balance in the body pursuant to the majority of the investigated parameters of spontaneous and induced chemiluminescence. This effect is more vividly expressed within early use with a prophylactic aim if compared to the use in the later stages of the process with visible changes in the antioxidant defence system of the body.

Results of a clinical study of Diart efficiency in treatment of early osteoarthritis of the knee.

Assessment of the treatment efficiency in terms of WOMAC index clearly showed the positive dynamics towards reducing the pain syndrome, morning stiffness and functional activity in patients of both clinical groups. In the main group the WOMAC index before the treatment amounted to (78.3 + 4.1) in 6 weeks of treatment a positive dynamics was noted - decrease by 2.4 times (33.5 + 4.7), and in 12 weeks of treatment there was a further, although small, positive dynamics - decrease by (27.9 + 2.6). In the comparison group there was a less pronounced, but similar dynamics within the WOMAC index (Table 5).

Evaluation of treatment results by visual analogue scale (VAS) of pain indicates a significant decrease in the intensity of pain in patients of both groups, but the stability of the clinical effect was different. Thus, in patients of the main group the pain intensity before treatment was (87.6 + 3.4) mm, in 6 weeks of treatment decreased almost by 4.5 times to (19.4 + 1.6) mm, and in 12 weeks despite the absence of treatment for about 1.5 months, continued to decline and amounted to (18.3 + 2.3) mm. Patients of the comparison group revealed a less evident dynamics of changes in pain intensity: before the treatment (86.6 + 2.8) mm, in 6 weeks - (24.7 + 2.5) mm, and in 12 weeks have not changed - (24.3 + 2.6) mm (Table 5).

The results of the functional status evaluation of the knee joint pursuant to the LYSHOLM scale in patients of the main group were significantly better if compared to other two groups. In 6 weeks subsequent to initiating the treatment the knee joint function increased from (21.4 + 4.6) to (86.4 + 5.7), and over the next 6 weeks continued to grow significantly and reached (87.6 +6 , 2). In the group of comparison during the first 6 weeks after initiating the treatment a positive dynamics was observed. There was an increase in joint function from (22.6 + 3.6) to (71,3 ± 4,8), but later there was a negative dynamics recorded - decreasing by (63.8 + 5.3), demonstrating instability of the clinical effect (Table 5). In addition, the study group in 12 weeks of observation revealed excellent results in 3.52% of patients, in contrast to the comparison group, where no excellent results were observed at all. This fact substantiated the advantage of Diart inclusion to the combined treatment of osteoarthritis of the knee joint in the early stages before the hyaluronate mono-drugs administration (Table 5).

Table 5

Dynamics of treatment results assessment in patients with osteoarthritis of the knee joint

Estimation parameters		Before treatment		In 6 weeks		In 12 weeks	
		main	comparison	main	comparison	main	comparison
WOMAC index		78,3 ± 4,1	75,4 ± 3,8	33,5 ± 4,7"	23,9 ± 2,3**	27,9 ± 2,6*	29,8 ± 1,9*
Visual analogue scale VAS of Huskisson, (mm)		87,6 ± 3,4	86,6 ± 2,8	19,4 ± 1,6**	24,7 ± 2,5**	18,3 ± 2,3*	24,3 ± 2,6*
LYSHOLM score scale (points)		21,4 ±4,6	22,6 ± 3,6	86,4 ± 5,7	71,3 ±4,8	87,6 ± 6,2	63,8 ± 5,3
LYSHOLM score scale (% of patients)	Perfect	-	-	-	-	3,52	-
	Good	-	-	77,7**	53,4**	82,9**	51,9**
	Satisfactory	65,3	68,5	19,2**	38,5**	12,1**	39,3**
	Unsatisfactory	34,6	31,7	3,00**	8,03**	1,3**	8,6**
Scale to determine the level of activity (in points) (TEGNER Activity Level scale)		2,6 ±0,2	2,3 ± 1,1	7,6 ± 1,2**	5,1 ± 0,8**	8,3 ± 0,6**	5,0 ± 0,9**
Assessment of treatment outcome by doctor (% of patients)	Ineffective	-	-	-	-	-	-
	Inadequate	-	-	-	7,6	-	15,8
	Satisfactory	-	-	30,4	72,8	26,3	70,5
	Good	-	-	55,1	16,3	58,3	13,5
	Perfect	-	-	14,4	3,1	15,3	-
Assessment of treatment outcome by patient (% of patients)	Ineffective	-	-	-	-	-	-
	Inadequate	-	-	-	8,8	-	16,7
	Satisfactory	-	-	33,4	76,3	19,7	79,4
	Good	-	-	57,8	13,5	69,3	3,7
	Perfect	-	-	8,6	1,2	10,9	-

Notes: * - $p < 0.05$; ** - $p < 0.01$ if comparing the values before and after treatment.

Determining the activity level pursuant to the Tegner scale showed a significant increase in activity of patients as early as 6 weeks after treatment in both groups (from (2.6 + 0.2) to (7.6 + 1.2) points), and in control (with (2.3 ± 1,1) to (5.1 + 0.8) point). In 12 weeks of observation in the study group the activity continued to increase (up to (8.3 + 0.6) points), while in the comparison group in 12 weeks of observation, it has not changed ((5.0 + 0.9) points) (Tab. 5).

According to the doctor's assessment 6 weeks after initiation of treatment in the study group an excellent clinical outcome was noted in 14.4% of patients, good - in 55.1% and satisfactory - in 30.4%. In 12 weeks of observation in the study group dynamics continued to slightly increase, while the comparison group experienced a slight setback in the received positive effect.

Subjectively patients showed fewer excellent results both in the main clinical group and in the group of comparison, while the number of good and satisfactory results increased, and at the end of the observation period in the study group the highest number of patients with good clinical results (69. 3%) was reached, while a satisfactory treatment outcome score dominated in the comparison group (79.4%) (Table 5).

CONCLUSIONS

The results of experimental and clinical studies have shown advantage of using the hyaluronate and sodium succinate combination in drug Diart versus hyaluronate mono-drugs in the treatment of patients with knee osteoarthritis on early stages, both in terms of pathogenetic validity of therapeutic effects and in terms of safety, extension and stability of the achieved clinical effect.

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