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COMPARISON OF TREATMENT WITH STEM CELLS OF WHARTON'S JELLY AND THE CLASSICAL COMBINED METHOD IN OSTEOARTHRITIS OF THE KNEE JOINT

Abstract. Osteoarthritis is one of the most common causes of chronic pain and disability in people worldwide. The trend towards an increase in middle age among the population in most European countries leads to an increase in the number of people who are faced with this disease. Thus, the aim of our study was to compare the results of the treatment with the stem cells of Wharton's cartilage and the classical combined method in people with osteoarthritis of the knee joint. In order to achieve the set goal, 30 people with primary diagnoses of osteoarthritis of the knee joint II-III stage were treated. with damage to one or both joints. Patients of the main group were injected with multipotent stem cells of Wharton's jelly obtained by the explant method. Patients of the control group received classical treatment, which included the injection of hyaluronic acid and physiotherapeutic procedures. MRI studies were performed on the patients and the clinical results of the treatment were evaluated according to the Knee Injury and Osteoarthritis Outcome Score (KOOS) scale. Statistical analysis of the obtained data was carried out in the license package "Statistica 6.0". A comparison of the obtained results regarding clinical symptoms and MRI data when using Wharton's jelly stem cells and the classical combined method in people with osteoarthritis of the knee joint during a year of observation showed that both at 3, 6 and 12 months in patients who received intra-articular stem cells from the source of which there were Wharton's jelly, significantly different ($p=0.05-0.00002$) values were observed regarding indicators of pain, symptoms,

function and daily activities, sports and active recreation, as well as quality of life compared to the control group that received classical treatment. In addition, patients who received intra-articular stem cells, the source of which was Wharton's jelly, had significantly different ($p=0.021$) values regarding the cartilage surface index of the medial femoral condyle and greater values of cartilage thickness in all observation periods except 7 months. All these data suggest that the use of mesenchymal stem cells, the source of which is Wharton's jelly, has significant advantages compared to the classical approach to the treatment of osteoarthritis.

Keywords: osteoarthritis, knee joint, mesenchymal stem cells, Wharton's jelly, physiotherapy treatment.

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ПОРІВНЯННЯ ЛІКУВАННЯ ЗА ДОПОМОГОЮ СТОВБУРОВИХ КЛІТИН ВАРТОНОВИХ ДРАГЛІВ ТА КЛАСИЧНОГО КОМБІНОВАНОГО МЕТОДУ ПРИ ОСТЕОАРТРОЗІ КОЛІННОГО СУГЛОБА

Анотація. Osteoarthritis є однією з найбільш поширених причин хронічного болю та інвалідності серед людей по всьому світу. Тенденція до зростання середнього віку серед населення в більшості країн Європи призводить до збільшення числа людей, які стикаються з цим захворюванням. Таким чином метою нашого дослідження стало порівняти результати проведеного лікування за допомогою стовбурових клітин вартонових драглів та класичного комбінованого методу у осіб з остеоартрозом колінного суглоба. Для досягнення поставленої мети проведено лікування 30 осіб з первинними діагнозами остеоартрозу колінного суглоба II-III ст. з ураженням або одного, або обох суглобів. Пацієнтам основної групи вводили мультипотентні стовбурові клітини вартонових драглів пупкових канатиків, отримані методом експлантів. Пацієнти контрольної групи отримували класичне лікування, що включало введення гіалуронової кислоти та фізіотерапевтичні процедури. Пацієнтам проводили МРТ дослідження та оцінювали клінічні результати лікування за шкалою Knee Injury and Osteoarthritis Outcome Score (KOOS). Статистичний аналіз отриманих даних проводили в ліцензійному пакеті "Statistica 6.0". Порівняння отриманих результатів щодо клінічних симптомів та даних МРТ при застосуванні стовбурових клітин вартонових драглів та

класичного комбінованого методу у осіб з остеоартрозом колінного суглоба протягом року спостереження показав, що як на 3, 6 так і 12 місяці у пацієнтів, що отримували внутрішньосуглобово стовбурові клітини джерелом яких були вартонові драглі спостерігалися достовірно відмінні ($p=0,05-0,00002$) значення щодо показників болі, симптомів, функції та повсякденної діяльності, спорту та активного відпочинку а також якості життя порівняно з групою контролю, що отримували класичне лікування. Окрім того пацієнти, що отримували внутрішньосуглобово стовбурові клітини, джерелом яких були вартонові драглі мали достовірно відмінні ($p=0,021$) значення стосовно показника поверхні хряща медіального виростка стегна та більші значення товщини хряща в усі періоди спостереження окрім 7 місяців. Усі ці дані свідчать на користь того, що застосування мезенхімальних стовбурових клітин, джерелом яких є вартонові драглі має значні переваги порівняно з класичним підходом до лікування остеоартрозу.

Ключові слова: остеоартроз, колінний суглоб, мезенхімальні стовбурові клітини, Вартонові драглі, фізіотерапевтичне лікування.

Statement of the problem. Osteoarthritis is the most common degenerative joint disease that affects one or more joints. Osteoarthritis can affect both small joints and large joints of the human body. For a long time, this pathology was not distinguished as a separate nosology, but considered as rheumatoid arthritis. Risk factors for the development of osteoarthritis include various endogenous and exogenous factors [1]. The pathogenesis of the development of this disease is complex and includes a part caused by the physical condition of the cartilage itself, its mechanical properties, the condition of the surrounding tissues, and inflammatory mediators released by the cartilage, bone, and synovial membrane [2].

According to approximate estimates, about 240 million people in the world have a symptomatic course of osteoarthritis. In Spain, survey data of people over 20 years of age showed that 29% of people have osteoarthritis of one or more locations [3]. As of 2019, osteoarthritis is considered a major global disease burden. This pathology makes up 7.1% of the burden of diseases of the human musculoskeletal system, which is much more than the indicators of 2007 and 1990. In addition, osteoarthritis of the knee joint is associated with an increased risk of premature death [4].

The prevalence of osteoarthritis increases significantly with age, which is associated with cartilage degeneration and a significant increase in the levels of reactive oxygen species, which leads to oxidative stress, disrupts specific cellular signaling pathways, resulting in impaired ability to maintain the extracellular matrix of cartilage and ultimately cell death [5].

The economic burden caused by osteoarthritis is steadily increasing every year and in the future (due to the aging of the population) may pose a serious problem for health care. Calculations by Canadian scientists showed that from 2010 to 2031, the total direct costs of this pathology will increase from 2.9 billion US dollars to 7.6 billion US dollars [6]. Knee arthroplasty alone increases direct lifetime costs by

an average of \$20,635 [7]. Thus, medicine is interested in finding new promising methods of treating osteoarthritis.

Connection of the publication with planned scientific research works. The article is a fragment of a research topic of the Department of Traumatology and Orthopedics of the National Pirogov Memorial Medical University, Vinnytsya "Improvement of methods of diagnosis, treatment and rehabilitation of patients with injuries and diseases of the musculoskeletal system" state registration number 0123U102765.

The purpose of the article – to compare the results of the treatment using Wharton's jelly stem cells and the classical combined method in people with osteoarthritis of the knee joint.

Research objects and methods. The results of the treatment of 30 patients who were treated at the VCCH EMA and the Vinprofimed clinic from 2018 to 2022 were analyzed. By gender, the patients were divided as follows: men – 12 (41.2%), women – 18 (58.8%). The study group included patients with primary diagnoses of II-III stage osteoarthritis of the knee joint. with damage to one or both joints. The clinical results of treatment were evaluated by the Knee Injury and Osteoarthritis Outcome Score (KOOS) at 3, 6 and 12 months after treatment.

Patients in the main group were injected intra-articularly with multipotent stem cells (MSCs) of Wharton's jelly umbilical cords obtained by the explant method.

For this purpose, umbilical cords were obtained during normal childbirth of clinically healthy women with a physiological course of pregnancy, at a gestation period of 39-40 weeks, with the voluntary consent of the mothers. A section of the umbilical cord with a length of 5-10 cm was washed with PBS, the vessels were mechanically removed. Wharton's jelly was mechanically crushed, the fragments were placed in a 75 cm² culture flask with aMEM nutrient medium with reduced glucose content, as well as with the addition of benzylpenicillin (2 units/ml), streptomycin (2 µg/ml) and 10% fetal calf serum. The first cells that migrated from the explant were observed at the bottom of the vial after 5-7 days. After 14 days, the number of cells was sufficient for reseeding. To obtain the following passages, the cells were subcultured after reaching a confluency of 70-80% using a solution of versene (0.02%) and trypsin (0.05%) in a ratio of 1:1. MSCs at the second passage were used for the experiment. To prepare the cells for injection, the culture was detached from the substrate using a solution of versene (0.02%) and trypsin (0.1%), after which the trypsin in the suspension was inactivated by adding an equal volume of the growth medium. The obtained suspension was processed in a centrifuge (1000 rpm). MSCs remaining in the pellet were resuspended in PBS and counted in a Goryaev chamber.

In all variants of experiments, MSCs were injected intra-articularly into patients at the rate of 25,000 cells per 25 µl of physiological solution, with a total volume of 2 ml per injection.

Two patients in the sixth month did not respond to the questionnaire, 1 year after the introduction of MSCs, the results of the questionnaires were received from 14 people.

Hyaluronic acid in a dosage of 60 mg (3 ml) was used to treat patients from the control group. Among the physiotherapeutic methods of treatment, 7-day cycles of shock wave therapy, iontophoresis, and laser therapy were used. Three patients did not respond to the questionnaire at the sixth month, 1 year after the injection of hyaluronic acid, the results of the questionnaires were obtained from 17 people.

We chose the thickness of the cartilage of the medial femoral condyle as the main indicator for evaluating the effect of mesenchymal stem cells, namely its change during the observation cycle in the main and control subgroups. MRI examination was performed before the start of treatment and within 3 to 6 months after the primary injections in the main and control groups of the study.

Statistical processing of the obtained data was carried out in the license package "Statistica 6.0". The Mann-Whitney U-test was used for a full integrated assessment of the clinical consequences of treatment according to the KOOS scale of two independent samples.

Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsya found that the studies do not contradict the basic bioethical standards of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant WHO regulations and laws of Ukraine.

Presentation of the main material.

Research results and their discussion. In general, 3 months after the start of treatment, 65.625% of excellent and good results are observed in the control group and 83.340% in the main group; after 6 months – 58.620% in the control group, 78.570% in the main group; after 12 months – 41.180% and 92.860%, respectively (table 1). In both treatment groups, there were no unsatisfactory treatment outcomes.

Table 1.

General evaluation of the results in the control and main groups.

		Observation period, months							
		3		6				12	
		Perfect	Good	Satisfactory	Unsatisfactory	Perfect	Good	Satisfactory	Unsatisfactory
Control	abs	2	19	11	-	1	16	12	-
	%	6,250	59,375	34,375	-	3,450	55,170	41,380	-
Main	abs	8	17	5	-	7	15	6	-
	%	26,670	56,670	16,670	-	25,000	53,570	21,430	-

Table 2 shows the results of the comparison of treatment of patients of the main and control groups in the time periods of 3, 6 and 12 months.

Table 2.

Evaluation of the dynamics of the KOOS scale in patients of the main and control groups.

Indicator	Quantity (main)	Quantity (control)	Term, months	U	Z	p
Pain	30	32	3	269,5	2,96	0,003
	28	29	6	207,5	3,16	0,002
	14	17	12	35,5	3,29	0,001
Symptoms	30	32	3	234,5	3,45	0,0006
	28	29	6	140,5	4,23	0,00002
	14	17	12	22,0	3,83	0,0001
Function and daily activities	30	32	3	286,5	2,72	0,007
	28	29	6	150,5	4,07	0,00005
	14	17	12	35,0	3,31	0,0009
Sports and active recreation	30	32	3	216,0	3,71	0,0002
	28	29	6	262,5	2,28	0,022
	14	17	12	51,5	2,66	0,008
Quality of life	30	32	3	340,5	1,96	0,05
	28	29	6	142,5	4,20	0,00003
	14	17	12	45,5	2,90	0,004

As can be seen from the obtained data, there is a statistically significant difference between the two study groups at 3, 6, and 12 months on five separate KOOS scales. This proves the high clinical effectiveness of the method of using mesenchymal stem cells in the treatment of initial and moderate manifestations of osteoarthritis of the knee joints, as well as the pronounced stabilization of the process during 1 year of observation.

The obtained values of changes in cartilage thickness among patients of the main and control groups during the observation period are shown in Figure 1.

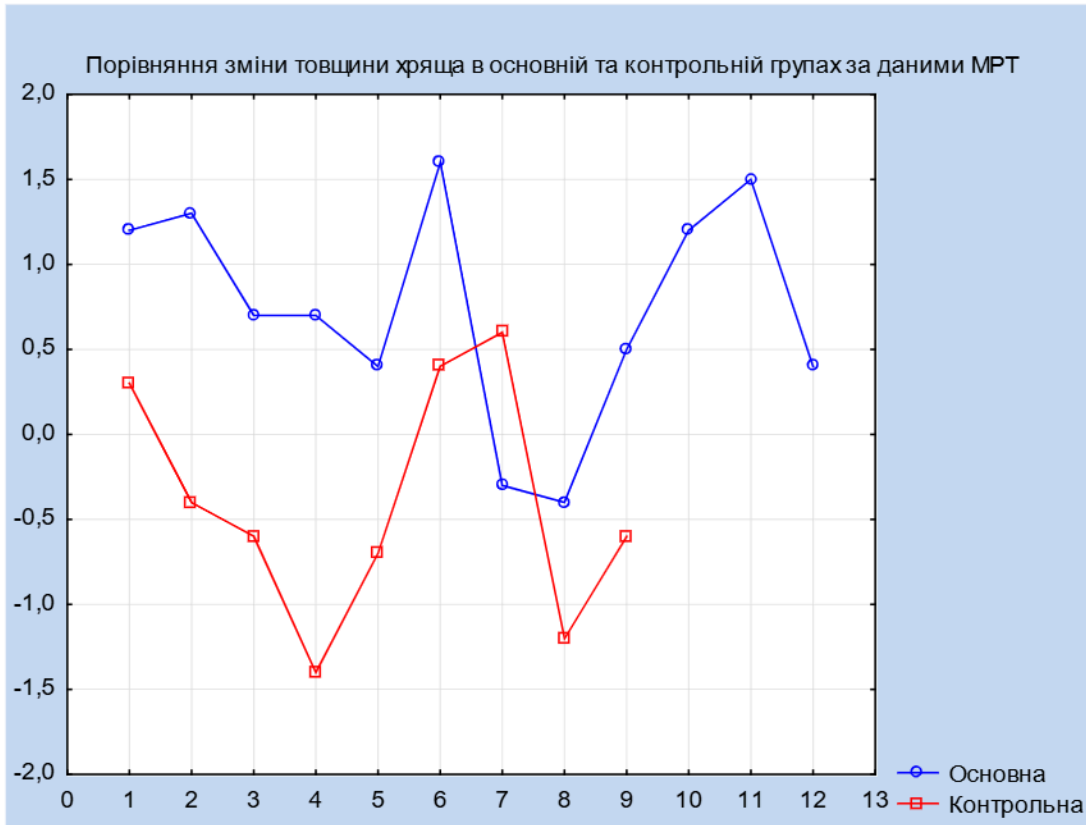


Fig. 1. Comparison of cartilage thickness values in the main and control groups. The red line is the control group. The blue line is the main group.

The presented data were also tested using the Mann-Whitney U-test and a statistically significant difference was determined in the change in the thickness of the cartilage covering of the medial femoral condyle of the patients according to the MRI data ($Z=3.06$; $p=0.002$). These data primarily indicate the influence of mesenchymal stem cells on the morphological structure of cartilage tissue, the restoration of cellular potential with the active construction of the cartilage matrix.

Evaluation of quality indicators according to tomogram data was carried out using Fisher's exact test. The main criteria were the cartilaginous surface of the medial femoral condyle, the presence of subchondral bone changes in the form of cysts and edema, joint swelling with effusion, and the presence of significant osteophytes (>4 mm). All data with statistical evaluation are shown in Table 3.

Table 3.

Tomographic analysis of the joints of the main and control subgroups.

	Sign	Main group (n = 12)	Control group (n = 9)	Statistical significance, p
The surface of the cartilage of the medial femoral condyle	The surface is intact (intact shiny plate)	12	5	0,021
	The surface is damaged (fibrillation, cracks)	0	4	
Changes in the subchondral bone	Intact	4	0	0,1
	Disturbed (edema, cyst formation)	8	9	
Swelling, effusion in the joint	Absent	7	3	0,39
	Present	5	6	
Formation of osteophytes	Absent	5	2	0,64
	Present	7	7	

The only parameter with a statistically significant difference ($p=0.021$) was the cartilage regenerate surface, which was obviously better in the main study group. Changes in the subchondral bone, as well as the formation of osteophytes, have a non-specific manifestation, and therefore do not regress during the study within six months. The inflammatory reaction of the joint in the form of edema and exudative reaction, in general, according to MRI data, is observed in both experimental groups ($p=0.39$). Although the edema in all cases is insignificant, there is no correlation, comparing with previous clinical data (dynamics of symptoms). In the future, this will require a special targeted evaluation with a larger number of raw tomogram data.

Thus, there is a statistically proven effect of intra-articular injections of Wharton's jelly mesenchymal stem cells in the treatment of gonarthrosis in comparison with the classical combined method of treatment involving hyaluronic acid and physiotherapeutic measures. The clinical evaluation of the proposed method is confirmed by the data of dynamic tomograms with a statistically significant increase in the thickness of the cartilage tissue of the medial femoral condyle and restoration of the cartilage surface. In comparison with standard methods, there is a progressive improvement in the well-being of respondents during 1 year of observation.

The most common questionnaires for assessing the quality of life in osteoarthritis, in addition to the one mentioned in our study, are the World Health Organization Quality of Life Group (WHOQOL-100), WHOQOL-Bref, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Arthritis Impact Measurements Scale (AIMS), and OA Knee and Hip QoL (OAKHQOL) [8]. When assessing the quality of life of elderly people suffering from this pathology, physical activity, the risk of falls, psychosocial consequences, sarcopenia, sexual health, urinary incontinence should also be taken into account [9].

A meta-analysis of 18 studies on the use of mesenchymal stem cells from bone marrow and adipose tissue (a total of 1069 knees) showed an improvement in the visual analog scale from 18.37 to 30.98 and 36.91, the mean WOMAC score from 25.66 to 25.23 and 15.60 and KOOS from 41.07 to 8.47 and 18.94 at 6 and 12 months, respectively, after cell therapy [10]. Similar results were obtained in another meta-analysis, where a statistically significant improvement of the visual analog scale and a decrease in WOMAC indicators were found in the 12-month and 6-month follow-up, respectively ($P < 0.001$ in both cases) [11].

Intra-articular injection of adipose-derived stem cells showed significant improvement in knee joint function over a 2-year follow-up period, as confirmed by WOMAC, VAS, and KOOS scores. Confirmation was also obtained by analyzing MRI images of the knee joint [12]. The same conclusion was obtained by performing a meta-analysis, where in 9 out of 11 studies, MRI evidence of joint cartilage restoration was found [13].

It is important to take into account the MOAKS and MOCART indicators during the MRI study of cartilage restoration. The results of clinical studies using stem cells show a significant improvement in the MRI picture compared to the control groups in the studies ($P < 0.001$ for both MOAKS and MOCART) [14]. MRI indicators T1rho, T2, T2star, R2star and ADC are also significantly different in the studied groups, which confirms the effectiveness of cell therapy [15].

Experimental studies on animals indicate a significant improvement in the results of the use of cell therapy when it is applied locally, namely intra-articularly [16].

Among the sources of stem cells that can be used for the treatment of osteoarthritis, significant interest of researchers is currently focused on the prospects of using Wharton's jelly. Currently, such studies are found both in the form of individual cases from practice [17] and in the form of controlled clinical studies [18]. However, preliminary data already show significant success in the use of cells of this origin in the treatment of osteoarthritis, which is consistent with our data.

Conclusions. A comparison of clinical symptoms and MRI data of Wharton's jelly stem cells and the classical combined method in subjects with osteoarthritis of the knee during one year of follow-up showed that:

- during the whole year of observation (3, 6 and 12 months) in patients who received intra-articular stem cells, the source of which was Wharton's jelly,

significantly different ($p=0.05-0.00002$) values were observed regarding indicators of pain, symptoms, function and everyday life activity, sports and active recreation, as well as quality of life compared to the control group that received classical treatment;

- during the entire year of observation (3, 6 and 12 months) in patients who received intra-articular stem cells, the source of which was Wharton's jelly, significantly different ($p=0.021$) values were observed in relation to the indicator of the cartilage surface of the medial femoral condyle and greater values of cartilage thickness in all periods observation other than 7 months.

Identified differences in the results of treatment indicate the advantage of treatment with the use of Wharton's jelly stem cells during one year of observation.

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