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Evaluation of the Efficacy of Magnetophoresis Transdermal Diclofenac Delivery in Patients with Knee Osteoarthritis

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Abstract

Osteoarthritis (OA) is a serious sociomedical problem, one of the leading causes of persistent disability and reduced quality of life. Modern publications on the use of transdermal drug formulations for OA evaluate the efficacy and safety of administration of an isolated drug. Pulsed magnetic field therapy is a modern method that allows for potentiation of the therapeutic effects of both the drug and the magnetic field (MF) within a single magnetophoretic technique.

Study Aim: To determine the effect of pulsed MF in terms of the clinical efficacy and tolerability of magnetophoretic transdermal diclofenac delivery in patients with gonarthrosis.

Materials and Methods The randomized placebo-controlled clinical trial enroled 65 patients with Kellgren-Lawrence grade 2-3 knee OA who were divided into 3 groups. In Group 1, which included 25 patients, diclofenac was delivered through magnetophoresis with the help of travelling MF (intensity — 20 mT, frequency 6.25 Hz, exposure — 20 min, mode No. 12); 20 patients from Group 2 were administering placebo — magnet therapy with diclofenac without the use of MF; 20 patients from Group 3 received pulsed low-frequency magnet therapy with travelling MF without local diclofenac therapy. During the examination the VAS and WOMAC scales, as well as EQ-5D questionnaire were used. The treatment results were analyzed using OMERACT-OARSI set of responder criteria.

Findings The combination therapy was found to produce a pronounced analgesic effect (according to VAS and WOMAC) in patients receiving magnet therapy ($p<0.01$), as well as a to cause significant reduction in stiffness and improvement in functional performance, which were more pronounced in patients who had been treated with magnetophoresis ($p<0.001$). The EQ-5D survey showed a positive effect of magnet therapy reflected in the change of the quality of life indicators. The analysis that included the OMERACT-OARSI criterion demonstrated a high rate (67.8 %) of response to magnetophoretic treatment with the application formulation of diclofenac.

Conclusion The magnetophoretic delivery of transdermal formulations of diclofenac with the help of pulsed low-frequency MF is effective, safe for patients with knee OA, and does not cause serious adverse events.

Keywords: *nonsteroidal anti-inflammatory drugs, diclofenac, transdermal formulations, knee osteoarthritis, traveling magnetic field, pulse magnetotherapy, magnetophoresis.*

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Osteoarthritis (OA) is a serious medical and social problem, one of the leading causes of permanent disabilities associated with the presence of a severe pain syndrome, functional disorders that lead to restrictions in mobility and reduced quality of life. Given the multifactorial nature of the pathogenesis of this disease, development of combination treatment approaches is a multidisciplinary task, the solution to which requires participation of many specialists: rheumatologists, therapists, pharmacologists, physiotherapists, trauma orthopaedists, developers and manufacturers of medical equipment. Despite the large number of therapeutic approaches

the effectiveness of the treatment in patients with OA remains unsatisfactory, which determines the urgent need to develop an effective combination therapy programs. The conventional treatment of joint diseases despite the high degree of evidence of its clinical effects is still dominated by pharmacotherapeutic approaches. Advances in theoretical pharmacology, especially the discovery of the mode of action of the drugs, as well as in synthetic chemistry and molecular biology, have significantly expanded the capabilities of pharmacotherapy.

In July 2014 [1], an algorithm for management of patients with knee OA in real clinical practice was published, consistently reflecting the basic principles of OA treatment. At the next ESCEO Congress in Paris in 2019, the recommendations were updated on the basis of the GRADE evidence system and new systematic reviews and meta-analyses.

According to current recommendations [1], treatment of patients with OA should be carried out using a combination of non-pharmacological and pharmacological methods. The combination use of medicines and physical factors is one of the modern branches of medicine. This is the reason for the increased interest of medical specialists to interdisciplinary issues, in particular, to the problem of interference in medicine, which is understood as the interaction and mutual influence of various therapeutic methods. It is assumed that the comprehensive effect of therapeutic factors should lead not only to summation of the effects, but to a qualitative leap in improvement of the therapy effectiveness. Pharmacophoresis is more of a concomitant form of application of physical and chemical factors [2].

There is evidence [3] that the epithelial and vascular permeability of the drugs, as well as their pharmacotherapeutic activity significantly increase under the influence of magnetic fields (MF). Therefore, MF can influence the intake of the drug applied topically. In addition to the increased penetration and transport activity, it is necessary to take into account the effect of the MF produced on the pharmacokinetics and pharmacodynamics of the drug.

The data from the systematic review and meta-analysis on the use of transdermal forms of nonsteroidal anti-inflammatory drugs (NSAIDs) in OA, presented in 2019, G. Honvo et al. [2] mainly refer to determination of the efficacy and safety of isolated topical administration of medicines. The publications on magnetophoretic delivery of NSAIDs are quite small in number, contain an insufficient amount of facts, characteristics, and comparison groups required for qualitative meta-analysis.

Currently, the introduction of combination physiotherapeutic and pharmacological methods into clinical practice requires conduct of preliminary applied scientific researches in order to form the necessary evidence base. First of all, it is necessary to solve the following issues:

- determine the range of medicinal substances, which are suitable and promising for pharmacophoresis;
- study pharmacokinetics and pharmacodynamics of the drugs exposed to physical factors;
- determine optimal forms of administration, concentrations of pharmaceuticals and parameters of physical factors for their concomitant use;
- compare the pharmacophoresis methods against each other, as well as against the traditional methods of physiotherapy and pharmacotherapy in terms of their effect;
- assess the medical and economic effectiveness of concomitant methods for different nosological entities [3].

The modern evidence-based model is guided by the databases of randomized multicenter placebo-controlled trials and employs analysis these databases to make clinical decisions and give recommendations. The recommendations, in turn, are created on the basis of assessment of the balance between the relative benefits and harms produced by the treatment, on the one hand, and significance of the treatment for the patient and his preferences on the other [4].

In this regard, the authors of the article conducted an experimental study on the effect of pulse MF produced on the physico-chemical properties of NSAIDs [5, 6]. The results of the experimental part of the study (IR spectroscopy, thixotropy, electron microscopy data) allowed us to conclude that it is possible to use pulsed MF and gel formulations of NSAIDs for magnetophoresis.

The aim of this study was to determine the effect of pulsed low-frequency MF on the clinical efficacy and tolerability of magnetophoresis delivery of the transdermal formulation of diclofenac in patients with knee OA.

Materials and Methods

We examined 65 patients with knee OA in day patient departments of the Ivanovo Regional State Hospital for War Veterans and the Ivanovo Regional Clinical Center for Medical Rehabilitation. All patients met the diagnostic criteria of OA of the American College of Rheumatology (ACR). *Inclusion criteria*: age over 18 years; diagnosed knee OA in the patient history — walking-evoked pain of at least 20 mm on the Visual Analog Scale (VAS), genology RENT stage lower than IV (Kellgren—Lawrence), OA duration of at least 2 years; signed informed consent.

Exclusion criteria: age under 18 years; OA X—ray stage IV (Kellgren—Lawrence); pronounced synovitis associated with OA; intra-articular injections during the period of the study; administration of glucocorticosteroids during the month preceding the start of the study; type 1 diabetes mellitus; rheumatological diseases in the active phase (rheumatoid arthritis, systemic lupus erythematosus, reactive arthritis); intolerance to diclofenac; presence of diseases and conditions that are considered as contraindications to magnet therapy (MT) in general and to the use "ALMAG".

A commercially produced of low-frequency pulsed MT device (travelling pulsed MT — TPMF) was used for magnetophoresis (magnetic induction — 20 mT, frequency — 6.25 Hz, exposure — 20 minutes per joint). Number of procedures — 12. The MT technique fully met the requirements of the clinical guidelines [7]. For the magnetophoresis, the gel formulation of diclofenac was applied to the area of the joint once a day in a single dose immediately before the procedure.

The patients were divided into 3 groups **(Table 1).** Group 1 included 25 patients aged from 53 to 82 years (mean age 65.33±6.9 years). The majority of the group were women — 18 (72 %) patients. The average duration of the disease

Table 1. **Characteristics of patients in three groups**

Age, years	65.33±6.9	73.94±7.8	66.5±5.9
40—50	5 (20 %)	2 (10 %)	6 (30 %)

50—60	8 (32 %)	6 (30 %)	–
60—70	6 (24 %)	6 (30 %)	9 (45 %)
70—80	6 (24 %)	6 (30 %)	5 (25 %)
Gender:			
males	7 (28 %)	5 (25 %)	6 (30 %)
females	18 (72 %)	15 (75 %)	14 (70 %)
Kellgren-Lawrence Grade Based on X-rays			
I	6 (24 %)	3 (15 %)	3 (15 %)
1			
II	10 (40 %)	9 (45 %)	8 (40 %)
2			
III	9 (36 %)	8 (40 %)	9 (45 %)
3			
Disease duration, years	12.62±5.2	12.38±2.5	8.12±3.4
Disease duration, years			
1—5	8 (32 %)	–	6 (30 %)
5—10	9 (36 %)	12 (60 %)	10 (50 %)
/	8 (32 %)	8 (40 %)	4 (20 %)
more than 10			

Characteristics

Age, years:

- Group 1 (n=25)
- Group 2 (n=20)
- Group 3 (n=20)

The X-ray examination showed that the group was dominated by patients with stage II—III OA (Kellgren-Lawrense) — 19 (76 %) patients. Patients from Group 1 received travelling MF magnetophoresis of the knee joint area with a pre-applied gel formulation of diclofenac (TPMF+diclofenac).

Group 2 included 20 patients aged 53 to 86 years with OA (mean age 73.94±7.8 years). The number of women in the group made up 75 %. The duration of the disease was 5-10 years in 12 (60 %) patients, more

than 10 years — in 8 (40 %); the average duration of the disease was 12.38±2.5 years. The X-ray examination revealed predominance of patients with stage II—III OA (Kellgren-Lawrense) in the group

— 17 (85 %) patients. Patients from Group 2 underwent placebo MT of the knee joint area performed with a pre-applied gel formulation of diclofenac (placebo MT+diclofenac).

Group 3 (comparison) included 20 patients aged 52-74 years (mean age 66.5±5.9 years). The group was also dominated by women — 14 (70 %) patients. The duration of the disease was 8.12±3.4 years on average. The X-ray examination revealed predominance of patients with stage II— III OA (Kellgren-Lawrense) — 17 (85 %) patients. Patients from Group 3 received only TPMF pulsed low-frequency MT without local diclofenac therapy.

Treatment efficacy evaluation: analysis of knee pain intensity using the Visual Analogue Scale (VAS) before and after treatment; determination of the dynamics using WOMAC scale (Western Ontario and McMaster Universities) and 4 parameters (pain, stiffness, functional activity, total

index); assessment of the x-ray dynamics using OMERACT-OARSI criteria, assessment of the dynamics of the quality of life using EQ-5D questionnaire.

Statistical processing was performed using Statistica Base 6.0 software. The arithmetic mean (M) and standard deviation were used to describe the features, and the Student's *T*-test was used to compare the dependent groups in terms of the quantitative variable. The differencies were considered consistent

at a significance level of $p<0.05$.

Findings

Nociceptive pain is one of the most common clinical syndromes of OA. When the effect of the treatment in terms of pain intensity was evaluated using the VAS scale, all groups showed a positive antalgic effect (Delta between the baseline and posttreatment values, as well as the percentage changes in baseline and posttreatment values), which was especially pronounced during the evaluation of dynamics of the "walking-evoked pain" and "stairs climbing-evoked" pain indices.

Table 2. **Dynamics of the "Walking-Evoked Pain" indicators (VAS and WOMAC) in Patients with OA during Treatment**

	/ Group 1		/ Group 2		/ Group 3	
Indicator	(*n*=25)		(*n*=20)		(*n*=20)	
at baseline		after treatment	at baseline	after treatment	at baseline	after treatment
at baseline		after treatment	at baseline	after treatment	at baseline	after treatment
VAS, mm movement-evoked pain	46.7	15.0* (68 %)	59.5	38.1**	42.0	34.0***
movement-evoked pain				(35.9 %)		(19.05 %)
/						
WOMAC, scores						
/	70.2	31.3*	116.8	83.1**	42.4	28.3**
Total pain rating						
/	29.1	10.0	40.5	27.4	16.2	10.0
stiffness						
/	77.5	68.63	67.81	65.26	62.1	52.2
functional failure						
Total rating	176.8	109.93	235.11	175.7	159.3	102.2

Indicator VAS, mm

total index

Note: * — $p<0.001$; ** — $p<0.05$; *** — $p>0.05$. The VAS scores in all groups show percentage changes in baseline and posttreatment values.

Note. * $p < 0.001$; ** $p < 0.05$; *** $p > 0.05$. The VAS scores in all groups show percentage changes in baseline and posttreatment values.

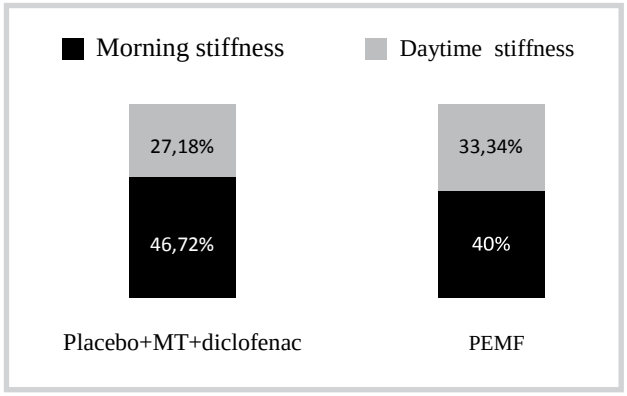

Fig. 1. **WOMAC Stiffness Dynamics in Patients with OA after a Treatment Cycle (% of Stiffness Reduction).**

The level of the analgesic effect was 1.5-2 times higher with magnetophoresis (TPMF+diclofenac) **(Table 2)**.

It is well known that the absolute advantage of the VAS scale is its simplicity and convenience, but it has a disadvantage — one-dimensionality (the patient records only the pain intensity). Therefore, it was considered appropriate to correlate the VAS values with the data of the WOMAC "pain" subscale. According to the recommendations of the American College of Rheumatologists (ACR) and the European League Against Rheumatism (EULAR), the efficacy of the therapy in patients with OA should be evaluated using the WOMAC scores. A decrease in the severity of pain (WOMAC) was observed in patients of all three groups, however, in the groups of patients receiving magnetophoresis, the antalgic effect was significantly more pronounced, which was expressed in a significant decrease in the pain index ($p<0.001$). The differences in the WOMAC absolute pain intensity decrease values between groups were significant both for each index of the scale (subscale) and for the total index. The obtained data serve as evidence of the symptom-modifying effect of both each of the components of the therapy and of their concomitant application (magnetophoresis).

When analyzing the WOMAC "stiffness" subscale during the treatment, we found significant differences between the indices of patients in the three groups. The changes in the total index were significant between Group 1 (magnetophoresis), Group 2 (Placebo-MT+diclofenac) and Group 3 (TPMF). By the end of the course of treatment the severity of stiffness had decreased in Group 1 by 68.35—81.2 % % (2 times), compared to the baseline. The study showed a decrease in the morning stiffness in Group 2 by 46.72 %, which was associated with the anti-inflammatory effect of NSAIDs **(Figure 1).**

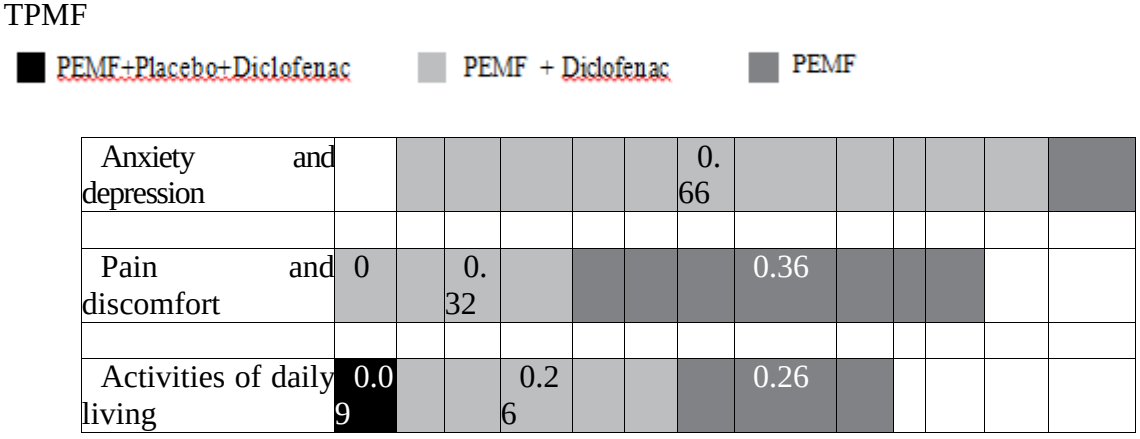

Fig. 2. **Status of Patients in the Three Groups According to EQ-5D Questionnaire (Delta) during Treatment (Delta, abs. value)**

In terms of the WOMAC "functional insufficiency" the best effect was also achieved in Group 1, where improvement was registered for all 17 activities listed in the subscale and amounted to 45.88—80.95 %. In Group 3 (TPMF) — only in 7 of the 17 analyzed indices improved. In Group 2, statistically significant improvements were registered for 1-2 indices, which indicates a significant impact on the functional capabilities of the used comprehensive method of exposure.

The analysis of the EQ-5D questionnaire data showed fairly positive dynamics of the final results compared to the baseline in the group of patients who received TPMF magnetophoresis and "ALMAG plus" device therapy: the most pronounced changes were registered for the "movement in space" and "anxiety and depression" indicators — by 29 and 36 % (0.58 and 0.66 points) respectively **(Fig. 2).** The obtained results were reliable in relation to the baseline (p<0.05). The analysis of the "health scale" values obtained after the course of treatment, showed increase in all three groups; on average, the final indicator was 69.89 points, i.e. 10.45 points higher than the baseline. The analysis of the follow-up groups showed the lowest increase (5.94 %) in Group 2 (MT-placebo+diclofenac), while in Group 1 (magnetophoresis), the index increased by 12.27 points (18.11 %) **(Table 3).**

The analysis of the obtained data according to the OMERACT-OARSI criterion showed a high (67.8 %) response to the transdermal NSAID magnitophoresis therapy, MT also showed a pronounced (52.23 %) response.

Table 3. **Comparative Assessment of Health Index Dynamics (%) in Patients with Knee OA According to the EQ-5D Questionnaire**

Health status (self-	Group 1		Group 2		Group 3	
assessment)	(n=25)		(n=20)		(n=20)	
	at baseline	after treatment	at baseline	after treatment	at baseline	after treatment
	67.73	80.0	62.1/	65.79	50.2	61.7
value, scores						
		12.27		3.69		11.5
Δ (increment to the baseline						
values)						
		18.11 %		5.94 %		15.23 %
% to the baseline value						
Confidence		p<0.02		p>0.05		p<0.05

Health status (self-assessment)

Significance

Based on the analysis of 65 case histories of the patients participating in the clinical trial, as well as according to the survey and examination of the knee joint area during 13 days of observation no unfavorable events or disadvantages of "ALMAG ACTIVE" were revealed, nor were there any complaints about the use of the transdermal formulation of the drug. The tolerability of both MT and magnetophoresis diclofenac delivery was generally good. There were no reasons for suspension or early termination of the study, as provided for in the plan, during the implementation of therapeutic measures and further analysis of the obtained results.

Discussion

OA treatment is symptom-modifying, aimed primarily at pain alleviation, stiffness reduction, and improvement of the joint functionality. Secondarily, as the pain decreases and functionality improves, the treatment facilitates somatic mobilization and improves the patient's quality of life. Most often, NSAIDs are used within a pharmacological therapy to reduce the severity of pain and inflammation. However, their comprehensive, often prolonged, use is associated with a wide range of adverse reactions, mainly in the form of a structural and functional impairment of the gastrointestinal tract and cardiovascular system, which can become the main factor limiting the therapeutic potential of these drugs [8].

At the same time, there is a growing interest for local

(topical) application of these medicinal products in OA patients. The local (topical) magnetophoresis delivery of NSAIDs allows the active ingredient to be delivered as close as possible to the source of pain without causing systemic exposure, which significantly reduces the risk of side effects and complications. The transdermal delivery route has many advantages, the drugs become not only easy-to-use and convenient, but also start to have a reduced risk of side effects due to the fact that the drug substance reaches the bloodstream and the target organ bypassing the gastrointestinal tract [9]. The capabilities of OA treatment have significantly expanded due to the development of transdermal therapeutical systems (TTS), which are a simple, convenient and safe pharmaceutical dose form. Tpday, 35 trade names of drugs produced in the form of TTS are represented in the Russian State Register of Medicinal Remedies, including TTSs containing diclofenac [10].

Magnetophoresis delivery of medicinal products is included in the Nomenclature of Medical Services (Order of the Ministry of Health of the Russian Federation No. 804n of 13.10.2017) (A.17.30.04), Section

"Medical Services that Represent Certain Types of Medical Interventions Aimed at Prevention, Diagnosis and Treatment of Diseases, Medical Rehabilitation and have an Independent Completed Value".

MF, being a physiological, well-tolerable method of physical exposure, interacts quite effectively with pther medications without affecting their structure and pharmacological properties, which allows it to be attributed to the group of physical enhancers — enhancers of pharmacological effect. In addition, MF (due to implementation of the primary effects of Lorentz and Hall) has its own symptom-modifying effect: it reduces pain and inflammation, improves blood supply and joint trophicity. It results in improved joint functionality and a lower number of restrictions on the main types of activities of daily living, which significantly improves the quality of life of the patient. This study has shown the effectiveness and safety of both the TPMF method and the combination exposure method employing the travelling MF from "ALMAG ACTIVE" and the gel formulation of diclofenac.

Conclusion

The results obtained during the multicenter randomized trial extend the evidence base of the effectiveness and safety of low-frequency pulsed MT in general and the travelling MF from

"ALMAG ACTIVE" in particular in patients with knee OA, as well as they prove the effect of the magnetophoresis delivery that increases the efficacy of transdermal formulations of NSAIDs in OA patients.

The authors declare that there is no conflict of interest associated with the publication of this article.

Authors declare there is no conflict of interests.

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