Original Research Article

EFFICIENCY OF THERAPY WITH HIGH CONCENTRATIONS OF TOPIC NSAIDs IN PATIENTS WITH HIP OSTEOARTHRITIS

ABSTRACT

Aims: The aim of the study was to evaluate the effectiveness of therapy with high concentrations of topical NSAIDs in patients with hip osteoarthritis, depending on the volume of local fat deposits.
Material and Methods: The study included 108 patients with a confirmed diagnosis of hip osteoarthritis. All patients were randomly divided into 2 large groups - according to the criteria for the volume of subcutaneous fat in the hip joint – patients with a skinfold thickness of 2 cm or less (group 1, n=68) and patients with a skinfold thickness of more than 2 cm (group 2, n=40). In addition, according to the used medication, the patients of each group were randomly divided equally into subgroups a (5% Ketoprofen gel) and b (5% Diclofenac sodium gel). The duration of treatment was 14 days. To assess the effectiveness of treatment, we studied the overall tolerability of the prescribed therapy, as well as the quality of life of patients at the time of inclusion in the study and after 14 days.
Results: In group 1 there was a significant improvement in the quality of life on all 5 scales of the questionnaire. When pairwise comparison of the studied parameters after the treatment, in the group of patients receiving the topical Diclofenac, the quality of life on all scales of the questionnaire was significantly better than in patients receiving Ketoprofen. All patients in group 2 showed a slight improvement in the quality of life in all parameters. The change in the studied indicators was not statistically significant and did not depend on the choice of topical NSAIDs.
Conclusion: Diclofenac has been shown to be more effective than Ketoprofen in patients with weak localized fat deposits. The efficiency of both drugs was insignificant in patients with pronounced fat deposits in the hip joint area.

Keywords: hip osteoarthritis; Ketoprofen; Diclofenac; high concentrations; localized fat deposits; quality of life.

1. INTRODUCTION

Hip osteoarthritis is one of the most common and disabling conditions in the elderly population [11]. Among people who have lived up to 85 years of age, the risk of developing symptomatic hip osteoarthritis is 25% [10], and indications for total hip arthroplasty in the end-stage of the disease occur in almost 10% of patients [2].

Despite the importance and urgency of the problem of hip osteoarthritis, studies of this pathology, as a rule, lagged behind studies devoted to osteoarthritis of the knee joint. Most likely, this is due to the significant prevalence of knee osteoarthritis [13] and its great visualization availability [6] and availability for clinical interventions. Clinical guidelines often combine hip and knee osteoarthritis [5, 8, 12], sometimes extrapolating results from knee studies to the hip joint.

At the same time, current recommendations are somehow different for osteoarthritis of these two localizations regarding the use of topical NSAIDs. Thus, according to the National Clinical Guideline Center, topical NSAIDs are effective only for knee osteoarthritis [12]. This is most likely due to the fact that the knee joint is located much closer to the skin and is more accessible for the penetration of NSAIDs applied locally.

In the modern scientific literature, there is no data on the efficiency of high doses of topical NSAIDs for the treatment of hip osteoarthritis. Also, we did not find studies that would demonstrate the effect of the volume of local fat deposits on the effectiveness of local treatment of this pathology.

The aim of the study was to evaluate the effectiveness of therapy with high concentrations of topical NSAIDs in patients with hip osteoarthritis, depending on the volume of local fat deposits.

2. MATERIAL AND METHODS

Prospective randomized single-blind study was approved by the Committee on Bioethics, National Pirogov Memorial Medical University, Vinnytsya, Vinnytsia, Ukraine. The Bioethics Committee considered that research was performed in accordance with the World Medical Association Declaration of Helsinki on the ethical principles for medical research involving human subjects, the Council of Europe Convention on the Human Rights and Biomedicine, relevant laws, orders of the Ministry of Health of Ukraine. Each subject of the study were provided with all details about medical procedures and given the opportunity to discuss any questions with healthcare professionals, and then signed a detailed form of informed consent to conduct the research.

The study included 108 patients with a confirmed diagnosis of hip osteoarthritis. There were 42 (38.9%) women and 66 (61.1%) men in the study. The average age of the patients was 62.4±10.3 years.

The inclusion criteria for the study were:

1. Age over 18 years old.
2. Confirmed diagnosis of hip osteoarthritis.
3. The onset of symptoms of the disease not earlier than 6 months before the study.
4. The impossibility of performing surgery to replace the hip joint due to severe concomitant pathology not related to the site of surgery, or because the patient's refusal of surgery.
5. No history of allergic reactions to the proposed NSAIDs.

The exclusion criteria from the study were:

1. Breastfeeding, pregnancy or pregnancy planning.
2. A history of other chronic inflammatory diseases or fibromyalgia.
3. A history of asthma, arterial hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, renal dysfunction or liver disease.
4. Surgery within 6 months prior to the start of this study.
5. A history of surgical interventions on the hip joints.
6. Concomitant use of acetylsalicylic acid (except for the constant administration of a low prophylactic dose to prevent heart disease) for at least 3 months prior to inclusion in the study without the possibility of discontinuation of the drug.
7. Use of warfarin or other anticoagulants within 30 days prior to selection.
8. A history of gastrointestinal bleeding or peptic ulcer disease.
9. A history of allergic reactions to the proposed NSAIDs.
10. The presence of infection and/or damage to the integrity of the skin in the area of the hip joint.
11. The presence of acute pathological conditions that threaten the patient's life.

12. Manifestation of chronic pathological processes.

13. Combined use of corticosteroid drugs (in any pharmaceutical form) or the use of these drugs within 30 days before enrollment in the study.

14. Use of any medicinal product in a research study within 30 days prior to enrollment in the study.

15. Development of allergic reactions when using the proposed drugs.

16. Development of pronounced side effects of the used drugs.

The diagnosis of hip osteoarthritis was established in accordance with the criteria developed by The American College of Rheumatology (Table 1) [1].

Table 1: **American College of Rheumatology criteria for the diagnosis of hip osteoarthritis [1]**

Clinical criteria A	Clinical criteria B	Clinical plus radiographic criteria
Hip pain AND Hip internal rotation <15° AND ESR ≤45 mm/h or hip flexion ≤115° if ESR unavailable	Hip pain AND Pain with internal hip rotation AND Morning stiffness of hip ≤60 min AND Over 50 years of age	Hip pain AND any 2 of the following: ESR <20 mm/h Radiographic femoral and/or acetabular osteophytes Radiographic joint space narrowing

Note. ESR – erythrocyte sedimentation rate.

In accordance with the objectives of the study, all patients were randomly divided into 2 large groups - according to the criteria for the volume of subcutaneous fat in the hip joint. Patients with a skinfold thickness of 2 cm or less (68 patients) were included in group 1. Patients with a skinfold thickness of more than 2 cm (40 patients) were included in group 2.

In addition, according to the used medication, the patients of each group were randomly divided equally into subgroups a and b. Patients of subgroups 1a and 2a received 5% Ketoprofen gel (Ketoprofen-Vertex, JSC VERTEX, Russia) locally 2 times a day. Patients of subgroups 1b and 2b received 5% Diclofenac sodium gel (Diclac®, Sandoz, Slovenia) locally 2 times a day. The duration of treatment was 14 days.

Skinfold thickness was measured as described by Soleiko [15].

To assess the effectiveness of treatment, we studied the overall tolerability of the prescribed therapy, as well as the quality of life of patients at the time of inclusion in the study and after 14 days.

Quality of life was evaluated based on the results of completing a specific questionnaire Hip dysfunction and Osteoarthritis Outcome Score (HOOS). The questionnaire consists of 40 questions, which are grouped into 5 scales: Symptoms, Pain, Function (daily living), Function (sports and recreational activities), Quality of Life.

The obtained data were processed using the statistical software package SPSS 20.0 for Windows. Data were presented as Mean ± Standard Deviation. Student's t-test with Bonferroni-Sidak correction and Analysis of Variance (ANOVA) were used to assess differences between parametric quantities. Wilcoxon T-test was used to compare the quality of life between groups. Mann-Whitney U-test was used to assess the dynamics of changes in quality of life within one group.

3. RESULTS

In general, in all patients, the use of both Ketoprofen and Diclofenac was tolerated normally and was not accompanied by significant adverse reactions. Systemic adverse reactions were not observed in any patient.

Local adverse reactions were manifested, as a rule, in the form of a skin reactions and did not correlate with the volume of local subcutaneous fat. So, when using Ketoprofen, the following were locally observed: hyperemia in 2 patients (3.77%), burning in 1 patient (1.85%), dry skin in 3 patients (5.55%). The use of Diclofenac was accompanied by hyperemia in 1 case (1.85%), burning in 1 case (1.85%), dry skin in 2 cases (3.77%). There were no statistically significant differences between the groups in terms of the number of adverse reactions. In all cases, the severity of adverse reactions was clinically insignificant, and all patients expressed a desire to continue participating in the study.

When assessing the quality of life before starting the use of drugs, the studied parameters in patients of all subgroups did not differ significantly. The indicators of the quality of life testified to the violation in all components of the quality of life, which were assessed using the questionnaire used.

Table 2 : **Quality of life in patients of subgroups 1a and 1b, depending on the used topical NSAID**

Topical NSAID	**Study timing**		
	Before	**After**	**p-value (Before vs. After)**
Symptoms			
Ketoprofen (1a)	37.94 ± 13.82	50.29 ± 14.51	p<0.01
Diclofenac (1b)	37.06 ± 13.82	57.79 ± 9.78	p<0.01
p-value (1a vs. 1b)	p>0.05	p<0.05	–
Pain			
Ketoprofen (1a)	39.85 ± 12.00	52.43 ± 13.12	p<0.01
Diclofenac (1b)	38.97 ± 11.01	60.88 ± 10.82	p<0.01
p-value (1a vs. 1b)	p>0.05	p<0.01	–
Function, daily living			
Ketoprofen (1a)	45.72 ± 9.42	55.80 ± 7.97	p<0.01
Diclofenac (1b)	45.29 ± 9.20	62.20 ± 9.46	p<0.01
p-value (1a vs. 1b)	p>0.05	p<0.01	–
Function, sports and recreational activities			
Ketoprofen (1a)	21.32 ± 9.87	27.02 ± 12.19	p<0.01
Diclofenac (1b)	21.69 ± 10.23	32.90 ± 12.15	p<0.01
p-value (1a vs. 1b)	p>0.05	p<0.05	–

Quality of Life			
Ketoprofen (1a)	29.60 ± 12.53	41.73 ± 17.73	p<0.01
Diclofenac (1b)	28.86 ± 12.41	50.37 ± 11.61	p<0.01
p-value (1a vs. 1b)	p>0.05	p<0.05	–

In the contingent of patients with a skin fold thickness in the hip joint area of 2 cm or less, there was a significant improvement in the quality of life on all 5 scales of the questionnaire. All patients, regardless of the drug used, noted an improvement in well-being, a decrease in the intensity of pain and in the severity of the general symptoms of the disease. It should also be noted that when pairwise comparison of the studied parameters after the treatment, in the group of patients receiving the topical Diclofenac, the quality of life on all scales of the questionnaire was significantly better than in patients receiving Ketoprofen.

Table 3: **Quality of life in patients of subgroups 2a and 2b, depending on the used topical NSAID**

Topical NSAID	**Study timing**		
	Before	**After**	**p-value (Before vs. After)**
Symptoms			
Ketoprofen (2a)	38.50 ± 15.82	40.25 ± 12.92	p>0.05
Diclofenac (2b)	37.75 ± 16.34	41.25 ± 13.07	p>0.05
p-value (2a vs. 2b)	p>0.05	p>0.05	–
Pain			
Ketoprofen (2a)	40.88 ± 12.86	43.38 ± 9.54	p>0.05
Diclofenac (2b)	39.38 ± 11.32	46.25 ± 9.51	p>0.05
p-value (2a vs. 2b)	p>0.05	p>0.05	–
Function, daily living			
Ketoprofen (2a)	47.57 ± 9.26	50.07 ± 7.96	p>0.05
Diclofenac (2b)	46.69 ± 9.03	51.54 ± 9.11	p>0.05
p-value (2a vs. 2b)	p>0.05	p>0.05	–
Function, sports and recreational activities			
Ketoprofen (2a)	21.88 ± 11.38	29.06 ± 14.66	p>0.05

Diclofenac (2b)	22.19 ± 11.73	30.31 ± 17.59	p>0.05
p-value (2a vs. 2b)	p>0.05	p>0.05	–
Quality of Life			
Ketoprofen (2a)	30.31 ± 12.87	37.81 ± 15.64	p>0.05
Diclofenac (2b)	29.06 ± 12.71	39.69 ± 17.12	p>0.05
p-value (2a vs. 2b)	p>0.05	p>0.05	–

All patients with a skinfold thickness in the hip joint area more than 2 cm showed a slight improvement in the quality of life in all parameters (Table 3). At the same time, the change in the studied indicators was not statistically significant. In addition, in this cohort of patients, the quality of life did not depend on the choice of topical NSAIDs.

4. DISCUSSION

This nature of the data obtained is explained by the fact that when the drugs are applied to the skin, the active substance penetrates to an insignificant depth without reaching the pathological focus, which corresponds to the previously obtained data in the study of knee osteoarthritis [12, 14]. A slight improvement in the studied parameters, in all likelihood, can be explained by the insignificant penetration of the drug into the pathological focus, local improvement in blood flow as a result of mechanical action during application of the drug.

As reported in the reference literature, the amount of topical drug that is absorbed through the skin is proportional to the area of its application and depends on the total dose of the drug used [3]. In obese patients, due to significant pronounced local fat deposits, the area of the skin in the projection of the joint increases relatively. This, in turn, leads to an increase in the amount of drug used required for application to a large area of the skin. After topical application of 2.5 grams of Diclofenac gel to the skin surface with an area of 500 cm2, the degree of absorption of Diclofenac is approximately 6% [3, 4]. An increase in the amount of applied gel and the percentage of the active substance leads to an increase in its concentration in blood plasma, and, accordingly, to an increase in its systemic effects, with comparable parameters of binding to blood proteins (99.7%), total systemic plasma clearance (263±56 ml/min) and plasma half-life (1-2 hours). For Ketoprofen, absorption into the systemic circulation is 5% of the total dose of the drug, with 99% binding to blood proteins and a plasma half-life of 17 hours [7, 9].

Since this study demonstrated the insignificant efficacy of the gel forms of Ketoprofen and Diclofenac in high concentrations in obese people, further scientific interest is to study the systemic and local effects of the studied drugs with an increase in the area of application, as well as the concentration and total dose of the applied active substance.

4. CONCLUSION

1. The use of high doses of topical Ketoprofen and Diclofenac in patients with hip osteoarthritis is characterized by good tolerance to both drugs and a low incidence of adverse reactions.

2. In patients with mild local volume of subcutaneous fat, the administration of topical Ketoprofen and Diclofenac in high concentrations can reduce the intensity of pain, reduce the severity of osteoarthritis symptoms, and improve the quality of life.

3. In comparison with Ketoprofen, the topical Diclofenac in high concentrations can significantly more effectively improve the quality of life of patients with hip osteoarthritis and poorly expressed local deposits of subcutaneous fat with a comparable number of adverse reactions.

4. The use of topical Ketoprofen and Diclofenac in high concentrations for the treatment of osteoarthritis of the hip joint is not indicated in patients with pronounced local deposits of subcutaneous fat due to their ineffectiveness in this category of patients.

5. From a scientific and practical standpoint, in the future, it is necessary to thoroughly study the correlation dependences of the systemic effects of the topical forms of Diclofenac and Ketoprofen, depending on the area of application, concentration and total dose of the applied active substance.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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