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The Comparative Efficacy and Safety of Long- and Short-Term Continuous Use of Non-Steroidal Anti-Inflammatory Drugs for the Treatment of Knee Osteoarthritis

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Abstract

The purpose — to compare the efficacy and tolerability of long-term and short-term continuous NSAIDs in patients with knee osteoarthritis with insufficient efficacy "on demand" NSAIDs and SYSADOA. ***Study design.*** 12-week, prospective, comparative, randomized, single-center study. ***Materials and Methods.*** 180 patients with primary knee osteoarthritis aged 40 to 85 years with insufficient efficacy of "on demand" NSAIDs and SYSADOA were examined. Anti-inflammatory drugs were recommended for everyone: 56 people took Naproxen (31.11%), 63 — Etoricoxib (35%), 61 — Ketoprofen (33.89%). Patients were randomized into two groups: 1st group — with 8-week continuous intake of NSAIDs, 2nd group — with a 2-week continuous course of NSAIDs. ***Results.*** There was a positive dynamics of pain syndrome according to VAS and decrease in the level of the WOMAC index in both groups after 2 weeks of therapy. The pain level (VAS) and WOMAC indices in 1st group achieved after 8 weeks significantly differed from the ones after 2 weeks of therapy (VAS dynamics —10.93±2.43 mm, t = 42.64; p<0.001). In both groups we noted gradual significant increase in the average pain level according to VAS and WOMAC indices after NSAIDs cancellation. However, there was better control of pain in 1st group with long-term NSAID than in 2nd one. Safety profile of drug therapy was similar in both groups. ***Conclusion.*** The long-term 8-week use of NSAIDs in patients with knee osteoarthritis with insufficient efficacy "on demand" NSAIDs and SYSADOA provides better dynamics of the pain syndrome than with 2-week therapy. After treatment is canceled longer prior NSAID therapy contributes to better control of the pain syndrome. Continuous use of NSAIDs demonstrated good tolerance and safety, did not require dose reduction and/or discontinuation of therapy. Thus, anti-inflammatory therapy of osteoarthritis in this group of patients may be prescribed for a longer period with continuous use of NSAIDs.

Keywords: knee osteoarthritis, non-steroidal anti-inflammatory drugs, NSAIDs.

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Introduction

Osteoarthritis (OA) is one of the most common diseases of the musculoskeletal system. According to various sources, up to 10% of the world's population suffer from it. It is expected that with an increase in population life expectancy in the coming years, OA may become the fourth most important cause of temporary disability [1, 2]. In the Russian Federation, according to official data, for the first time, OA as a primary diagnosis is annually established in 600,000 patients [3]. Given that all joints components and tissues are involved in the pathological process, OA leads to the development of pain, limitation of joints mobility, deterioration in patients quality of life, and often to disability. The material costs of medical care providing, including joint replacement, result in a significant social and economic burden for the country's healthcare system [4]. The prevalence of knee and/or hip OA in various populations, depends on the research method option and, according to some authors, ranges from 2 to 42% by only clinical criteria, 16–33% — by only radiological, and 1.5–15.0% — by a combination of these two methods [5]. According to epidemiological studies, OA affects up to 13% of the population over 18 years of age [6]. Thus, the development of methods which increase the effectiveness of OA treatment remains rather relevant.

One of the most effective drugs in the treatment of OA are non-steroidal anti-inflammatory drugs (NSAIDs) [7]. They exert anti-inflammatory, analgesic effects, and are the most affordable class of drugs. Nowadays, it is considered proven that the leading pathogenetic mechanism of OA is chronic low-grade inflammation, supported by tissue cytokines [7, 8, 9]. Thus, the class-specific suppression of inflammation by drugs of this group is quite justified. However, the potential risks of serious side effects limit the possibility of long-term use of NSAIDs. Nevertheless, to date, it has been shown in a number of clinical studies that long-term continuous use of NSAIDs allows achieving somewhat greater control of the pain syndrome than short-term courses [1, 10, 11]. In real clinical practice, there are patients in whom short-term NSAID therapy courses lead to the early resumption or intensification of pain [12].

It can be assumed that in order to increase the effectiveness of anti-inflammatory therapy of OA in these patients, the treatment should be carried out with longer courses of NSAIDs. However, many questions remain, and additional studies of various prescribing regimens of drugs of this class are required in order to optimize the ratio of benefit and risk.

The purpose of the study was to compare the efficacy and tolerability of long-term and short-term NSAIDs continuous administration in the knee OA patients previously took NSAIDs "on demand" with slow-acting symptomatic agents for treating osteoarthritis (SYSADOA).

Materials and Methods

The study design

A 12-week, prospective, comparative, randomized, single-center study to evaluate the efficacy and safety of long-term continuous NSAIDs taking as the first-line treatment for knee OA.

The study planning

At the beginning, an analysis of outpatient records of 500 patients with OA was performed in order to control the prescribed drugs of the NSAIDs group in real clinical practice. It was found that choice of a particular type of NSAIDs administration to the OA patients depended on the risk of drug taking complications: the OA patients with a high risk of GI complications were prescribed etoricoxib, with a high CV risk — naproxen, in the absence of concomitant pathology — ketoprofen. Based on these data, in order to adopt as much as possible the study to real clinical practice, it was

Etoricoxib, Naproxen, and Ketoprofen that were included in the treatment scheme of the planned study.

The study conduction

200 patients with OA were offered participation in the study. 180 patients signed a written consent to take part in the study. The sample response rate was 90.9%.

Patients included in the study were treated on an outpatient basis by rheumatologists. Prior to the study, the patients received NSAIDs as needed and drugs of the SYSADOA group for at least 3 months without pronounced clinical effect. The patients were randomly divided into two groups of continuous NSAIDs administration by computer-generated simple random sampling: the 1st group with an 8-week course and the 2nd group with a standard 2-week course. The NSAIDs choice was determined by the patients concomitant pathology, although, with the uniformity of the groups. Naproxen was recommended to 56 (31.11%) patients, etoricoxib — 63 (35.00%), ketoprofen — 61 (33.89%). Quantitative data with a normal distribution are presented as M±SD, with non-normal — as Me (Q1–Q3).

Inclusion criteria:

1) an established diagnosis of primary knee OA according to the ACR criteria (R. Altman et al., 1986);

2) the patients age from 40 to 85 years;

3) the absence or low effectiveness of NSAIDs in the "on demand" mode + SYSADOA drugs;

4) signed informed consent.

Exclusion criteria:

1) secondary gonarthritis — infectious arthritis, systemic inflammatory joint diseases, gout, pseudogout, Paget's disease, intraarticular fractures, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary chondromatosis;

2) aseptic necrosis of the femoral and tibial condyles;

3) surgical interventions on the knee;

4) concomitant serious illnesses (uncontrolled arterial hypertension, unstable angina pectoris, CV failure, type 1 diabetes mellitus, severe liver and kidney disease);

5) the presence of acute or exacerbation of chronic peptic ulcer of the stomach or duodenum during the last month.

The study was carried out in three stages.

The first stage (14 to 16 days): selection of patients and the period of "purifying" from the previous therapy (at least 14 days). Visit 1 — confirmation of the diagnosis, exclusion from NSAID therapy for 14 days.

The second stage (visit 2): randomization of the patients into a group with 8-week continuous intake of NSAIDs (n = 90) and a group with a 2-week course of the therapy (n = 90). Assessing the level of pain by VAS, the clinical and functional index of WOMAC, laboratory parameters of liver and kidney function, blood pressure dynamics, the need to change antihypertensive therapy.

The third stage (visits 3, 4 and 5) at the 2nd, 8th and 14th weeks from the therapy initiation moment, respectively, when the level of pain by VAS, the clinical and functional WOMAC index, laboratory parameters of liver and kidney function, the dynamics of blood pressure and the need to change antihypertensive therapy were redetermined.

The criteria for assessing the effectiveness of the therapy:

1) the dynamics of pain intensity in the joints during therapy on the VAS in mm;

2) dynamics of the WOMAC index (pain, stiffness and functional impairment) in points, against the background of therapy.

Therapy safety assessment:

1) recording of dyspeptic complaints;

2) control of hepatic aminotransferases and total bilirubin level;

3) control of creatinine and blood urea level;

4) recording complaints of increased blood pressure and heart rate;

5) monitoring blood pressure and heart rate in the dynamics, required the change in the antihypertensive therapy.

Statistical analysis

Statistical data processing was performed using the STATISTICA 10.0 software package for Windows. The patients were randomized into 2 groups using a computer randomization generator. The distribution normality was assessed by the Kolmogorov-Smirnov test. All quantitative indicators, with the exception of age and subscales of the WOMAC index such as pain and stiffness, were subject to normal distribution testing. For intergroup analysis, the Student t-test (in the case of a normal distribution) and the Mann-Whitney U-test (in the case of a non-normal distribution) was used. To assess the dynamics of the studied indicators, the Student t-test was employed.

Results

Both patients groups were comparable by age, gender, disease duration, baseline pain level according to VAS, and the total WOMAC index. The clinical characteristics of the patients are presented in the Table.

The table shows that, before treatment, the compared groups of patients with an 8- and 2-week NSAID course did not have statistically significant differences in gender, age, OA characteristics and comorbidity ($p>0.05$).

All the patients were prescribed NSAIDs. In the group with a constant 8-week NSAIDs taking, naproxen was administered to 27 (30.0%) people, etoricoxib to 31 (34.5%),

Table

Clinical characteristics of the patients at the time of inclusion in the study

Indicators	Group with an 8-week NSAIDs course, n = 90	Group with a 2-week NSAIDs course, n = 90	p
Age, years	61 (54–73	60.5 (54–69)	0.76
Gender, M/F, n	17/73	18/72	0.85
Duration of the disease, years	6.98±5.42	7.11±5.71	0.87
The initial pain level by VAS, mm	46.9±10.43	47.35±10.44	0.78
Initial WOMAC total index, points	34.03±7.63	34.51±7.78	0.49
WOMAC subscales, points			
Pain	11 (9–13)	10 (8–13)	0.34
Stiffness	4 (2–5)	4.5 (2–6)	0.11
Impaired function	25.55±10.31	26.45±10.93	0.6
Comorbidity, n (%)			
Arterial hypertension	52 (57.7%)	53 (58.8%)	0.88
Coronary heart disease	19 (21.1%)	18 (20%)	0.85
Atherosclerosis	63 (70%)	60 (66.6%)	0.62
Type 2 diabetes	14 (15.5%)	12 (13.3%)	0.67
Chronic kidney disease	3 (3.3%)	2 (2.2%)	0.65
COPD	12 (13.3%)	13 (14.4%)	0.83
Gastrointestinal diseases	4 (4.4%)	4 (4.4%)	1
Obesity	49 (54.4%)	53 (58.8%)	0.55

ketoprofen to 32 (35.5%). In the group with a 2-week course of NSAIDs, naproxen was taken by 29 (32.2%) people, etoricoxib — by 32 (35.5%), ketoprofen — by 29 (32.2%).

To select the method of statistical analysis, the normality of indicators distribution after 8 and 14 weeks of NSAIDs courses was assessed. The dynamics of the indicators level by VAS is presented in Fig. 1.

As can be seen from Fig. 1, after 2 weeks therapy, a positive dynamics of pain syndrome was shown in both groups. In the group with a 2-week course, after NSAIDs withdrawal, a gradual statistically significant increase in the average VAS pain level occurred (6 weeks after the start of the study, the dynamics of VAS was 5.57±1.23 mm, t = -43.02; p<0.001). In the group of patients with an 8-week course, against the background of a longer use of NSAIDs, the better control of the pain syndrome was noted. VAS pain level in 8 weeks after the start of the therapy significantly differed from the level achieved after 2 weeks treatment (VAS dynamics: 10.93±2.43 mm, t = 42.64; p<0.001). In 6 weeks after the NSAIDs discontinuation, the 1st group demonstrated a slight increase in the average VAS pain level (dynamics: 2.04±0.45, t = 42.63; p<0.001). Although, the changes were significantly less pronounced than in the 2nd group (t = 25.53, p<0.001).

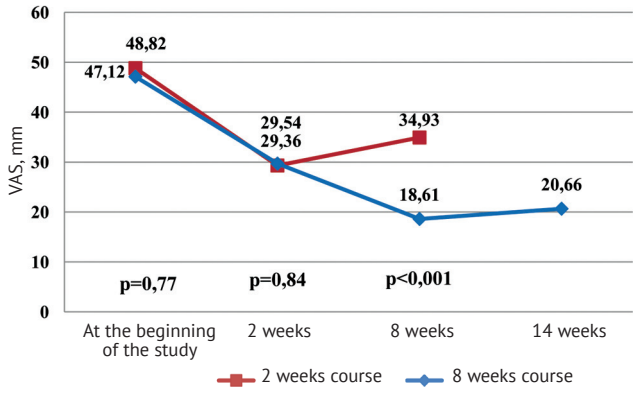

Fig. 1. The dynamics of the pain average according to the VAS index for the entire observation period and the statistical significance of intergroup differences.

To select the method of statistical analysis, the normality of the WOMAC indicators distribution was assessed. As was mentioned above, the baseline WOMAC level in groups with continuous NSAIDs taking and "on-demand" was comparable. The dynamics of the WOMAC index during the study is presented in Fig. 2.

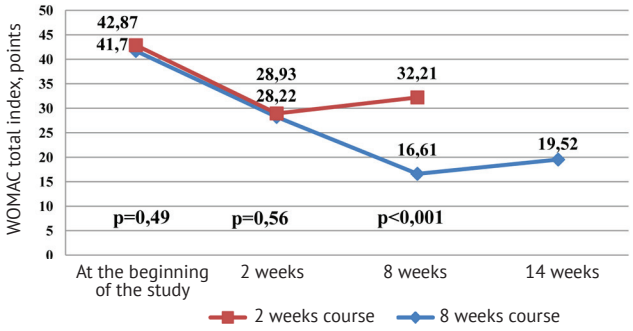

Fig. 2. The dynamics of the WOMAC average for the entire observation per.

As can be seen from Fig. 2, in both groups after 2 weeks therapy, a decrease in the average level of the WOMAC total index was noted. The average subscales of the WOMAC total index in both groups were comparable in the 2nd week of the therapy:

1) pain: in the 1st group 6.5±1.89 vs. 6.31±1.87 in the 2nd group (p = 0.35);

2) stiffness: 2.11±1.18 vs. 2.43±1.23, resp. (p = 0.09);

3) dysfunction: 18.47±7.61 vs. 19.03±7.87, resp. (p = 0.64).

In the group of the patients with 2-week NSAIDs taking after discontinuation of the therapy, a gradual statistically significant worsening occurred (in 6 weeks the dynamics of the WOMAC was 3.27±0.75, t = -41.72; p<0.001). In the group of the patients with 8-week NSAIDs taking, the further decrease in the average level of the WOMAC total index occurred. WOMAC total index in 8 weeks after the start of the therapy, significantly differed from the level of 2 weeks treatment (WOMAC dynamics total 11.61±3.14 mm, t = 35.07; p<0.001).

In 6 weeks after NSAIDs discontinuation in the 1st group there was also a slight increase in the average level of WOMAC total (index dynamics -2.91±0.84, t = -32.51; p<0.001), but it was significantly less pronounced than in the 2nd group (t = 3.08; p = 0.0023).

The safety assessment. In both groups, a similar tolerance profile of drug therapy was observed. The exceeding of the upper limit of ALT, AST and total blood bilirubin was clinically insignificant (no more than the two upper limits of the norm) and was comparable in both groups: 6 (6.6%) patients in the group with 2-week NSAIDs taking and 7 (7.7 %) patients in the group with 8-week taking. The exceeding of the upper limit of the normal level of urea and blood creatinine was not noted.

In 12 patients, 7 (7.7%) in the 1st group and 5 (5.5%) in the 2nd group, dyspeptic complaints occurred during therapy. 5 patients complained of discomfort in the epigastrium, 3 — of nausea, 3 — of heartburn, one patient complained of loose stool. In all the cases, the normalization of the diet led either to the disappearance of these complaints, or to a significant improvement in how they feel themselves. Therefore, it is impossible to confirm the direct role of the therapy in the occurrence of mentioned conditions.

5 patients had episodes of arterial hypertension, 3 (3.3%) in the 1st group and 2 (2.2%) in the 2nd. The episodes were corrected by the additional use of short-acting antihypertensive drugs. In the 2nd group, one episode of dyspnea was detected (1.1%).

Discussion

According to official data, from 2000 to 2010, the number of patients with OA in the Russian Federation increased by almost 2.5 times [2]. The leading reason for contacting the rheumatologists of our institute by the OA patients was joint pain.

Given that the leading role in the pathogenesis of OA belongs chronic low-intensity systemic inflammation, anti-inflammatory therapy should be a key element of OA therapy [7, 8, 9]. It has been proved that all NSAIDs have equal analgesic potential and their effectiveness depends on the dose, the higher doses provide a more pronounced effect [13, 14]. NSAIDs are recommended to be prescribed in the minimum dose for the shortest possible time, taking into account the patient's comorbid conditions and the safety profile of these drugs [15, 16]. Thus, according to ESCEO recommendations, if there is a risk of CV complications, naproxen and ibuprofen, a low dose of celecoxib (200 mg a day) should be preferred over diclofenac. If there is a risk of adverse events from the GI tract, coxibs are recommended [17]. There is also evidence of high efficacy and safety of etoricoxib compared with meloxicam in the gonarthrosis treatment[15].

A preliminary analysis of the outpatient records of 500 patients with, OA which we conducted at the Zborovskiy Scientific Research Institute of Clinical and Experimental Rheumatology, showed that in real clinical practice, patients with a high risk of GI complications were most often prescribed etoricoxib, with a high CV risk — naproxen, in the absence of concomitant pathology — ketoprofen. These data determined the spectrum of drugs included in this study.

In recent years, there has been increasing evidence that prolonged continuous use of NSAIDs in OA in some cases can reduce the rate of relapse of the disease, and also provides better control of symptoms than taking them "on demand" [6]. The authors assessed the effectiveness of NSAIDs in 7 to 14 days of the therapy [10]. However, in real clinical practice, it is often happens that the patients on short-term NSAIDs develop the early relapse or pain intensification [12].

According to our study, the prolonged use of NSAIDs in the patients with gonarthrosis, who previously took NSAIDs "on demand" with simultaneous SYSADOA administration, led to a more pronounced and persistent pain reduction. Even after discontinua-

tion of therapy in the patients who received the continuous NSAIDs courses, the analgesic effect persisted for a longer period. Thus, in the group with 2-week therapy in 4 weeks after discontinuation of NSAIDs, a significant increase of pain level was observed by the VAS: 5.57±1.23 mm (t = –43.02; p<0.001), by the WOMAC total: 3.27±0.75 index (t = –41.72; p<0.001). In the patients with 8-week NSAIDs, better pain control was observed, and only in 6 weeks after the therapy discontinuation there was some increase in pain according to VAS: 2.04±0.45 (t = -2.63; p<0.001). Although, it was accompanied by a further decrease in the average WOMAC total: 11.61±3.14 mm (t = 35,07; p<0.001). In addition, the continuous use of NSAIDs showed good tolerance and safety in relation to the GI, CV and kidneys. It did not require a dose reduction and/or discontinuation of the therapy.

Conclusion

The data of our study suggest that anti-inflammatory therapy with NSAIDs in the OA patients should be prescribed for a longer period (at least several weeks) with continuous medication taking.

Publication ethics

Patients gave voluntary informed consent to participate in the research study.

Conflict of interest: The authors declare no conflict of interest.

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Authors' contributions

B.V. Zavodovskiy — research concept and project development, direct management of the project team.

E.V. Papichev — data statistical processing, tables and figures.

L.E. Sivordova — literature data analysis, text preparation.

Yu.V. Polyakova — text preparation.

Yu.R. Akhverdyan — outpatient records maintenance, entering records into the database, data statistical analysis.

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