Introduction

Pain is a common reason for seeking medical help all over the world. In accordance with the Global Pain Index Report (Global Pain Index Study) in 2020, 34% of the world’s population experienced chronic pain of different localization, among which every fifth person was under the age of 30 [1]. Among the young people (18-34 years old), the most widespread type of pain is muscular, while among middle-aged and elderly persons (over 55 years old), pain in the joints occurs more often [2].

The most common cause of joint pain is osteoarthritis (OA). As a result of its progression, all structural elements of the joint (cartilage, synovial membrane, capsule, subchondral bone, etc.) are involved in the process [3]. The incidence of OA increases with age and its prevalence among the female population is higher than among males. In the structure of the diseases of the musculoskeletal system, the frequency of knee OA is two times higher than hands and hip OA. The tendency towards an increase of the number of OA cases persists until the age of 80 years old, and among the persons of senile age and long-lived people, a slight decrease in the frequency of damage to all groups of joints is observed [4]. During the last 20 years, the prevalence of OA in the world had been increased by almost 65%, and the number of visits to primary care physicians reaches 4 million per year [5].

Comparative evaluation of the effectiveness of parenteral and oral forms of diclofenac sodium and meloxicam in patients with symptomatic osteoarthritis of the knee joints


Abstract. Nonsteroidal anti-inflammatory drug are considered at the cornerstone drug therapy for osteoarthritis (OA) because their main function is to relieve pain and reduce inflammation. The aim of the study was to compare the efficacy of treatment of patients with symptomatic knee osteoarthritis (KOA) using the diclofenac sodium and meloxicam. Materials and methods. The study included 40 females aged 50–75 years with symptomatic KOA, and were divided into 2 groups: group I — 20 subjects receiving diclofenac sodium; group II — 20 subjects receiving meloxicam. The intensity of the pain syndrome and the functional of the knee were assessed using the WOMAC scale, the four-component VAS, the Lequesne index, and functional tests at each visit. The safety of medication was determined by the frequency adverse events. Results. Patients of two groups did not differ by age and initial level of knee pain. During the treatment, patients in both groups showed a reduction of pain intensity by VAS on 5 and 20 days of therapy (p < 0.01) without significant difference between groups, however in the subjects of group I the level of pain intensity by VAS on days 2 and 3 of treatment was significantly lower compared to group II (p = 0.003 and p = 0.03, respectively). In patients of both groups were revealed a significant reduction of pain, stiffness and physical function by WOMAC subscales on 5 and 20 days of treatment, but in group I the intensity of pain after 5 days of treatment was significantly lower (t = 2.8, p < 0.004) compared to group II. Conclusions. The treatment of patients with knee OA using the diclofenac sodium and meloxicam is effective, but in the case of diclofenac sodium analgesic effect were faster, already on 2 and 3 days of treatment were detected significantly lower pain intensity by VAS and on 5 days by WOMAC pain subscale. Keywords: knee osteoarthritis; diclofenac sodium; meloxicam
Apart from the main complaint of the patients for the pain, the symptoms of knee OA vary from mild stiffness to a pronounced change in gait and movement limitations. Treatment of OA is a long-term process, which should be based on the principles of evidence-based medicine [3]. However, there are currently no effective methods of the treatment that can provide patients with a full recovery. OA therapy should be comprehensive and include non-pharmacological approaches, pharmacological treatment methods and, if necessary, surgical procedures [6].

For the treatment of this pathology, non-steroidal anti-inflammatory drugs (NSAIDs) are most often prescribed. Their use is recommended in all relevant international and domestic guidelines for the treatment of the patients with OA of various localization. It is important to remember that it is recommended to use NSAIDs in the lowest effective doses during the shortest possible period of time, and for the patients with an increased risk of gastrointestinal complications, gastroprotective measures should be used [6]. NSAIDs are considered to be the cornerstone of drug therapy for OA, as their main function is to provide relief of pain and reduction of the inflammation [7].

The purpose of the study was the comparison of the effectiveness of the treatment of the patients with symptomatic knee OA with drugs of Diclofenac sodium and Meloxicam.

Materials and methods

At the Department of clinical physiology and pathology of the musculoskeletal system of the State Institution "D.F. Chebotarev Institute of Gerontology of the National Academy of Sciences of Ukraine" a prospective, randomized, open, active-controlled study in two parallel groups was conducted, which had been approved by the Ethics Committee of the above-mentioned institution (protocol No. 36/20 dated 17-th of December, 2020).

The study was conducted in accordance with the terms of the Declaration of Helsinki. Before starting the screening procedures, the subjects obtained the informed consent signed by the patients themselves to participate in it. Patient identification information was processed only by the authorized personnel and stored in the locked cabinets accessible only to the research personnel.

The study included 40 women with symptomatic knee OA of the II-III degree according to Kellgren-Lawrence scale. The criteria of inclusion were:

1. women in the postmenopausal period at the age of 50-75 years old;
2. the duration of clinically and radiologically confirmed knee OA no less than 3 months;
3. expressiveness of the pain syndrome > 40 mm according to the visual analog scale (VAS) for the time of inclusion in the study;
4. body mass index (BMI) ≤ 35 kg/m².

The exclusion criteria from the study were: hypersensitivity to diclofenac sodium or meloxicam or to other components of drugs or to active substances with a similar effect; the presence of symptoms of asthma, angioedema or urticaaria after taking NSAIDs; previous bleeding from the gastrointestinal tract or perforation; active peptic ulcer, acute or severe cardiovascular failure, impaired liver and kidney function. In addition, the exclusion criteria included taking other NSAIDs within 2 weeks or glucocorticosteroids within 4 weeks before the inclusion in the study and taking symptomatic slow acting drugs for osteoarthritis (SYSA-DOA) within 2 weeks before the start of participation in the study.

The patients who met inclusion criteria and did not have exclusion criteria had been enrolled and randomly assigned to group I or group II. Patients of both groups have received standard non-drug therapy for OA (physical therapy, use of knee braces if necessary).

Group I included 20 subjects who had received intramuscular injections of diclofenac sodium (Dicloberl®) 75 mg (3 ml) once a day during 5 days, followed by oral administration of diclofenac sodium (Dicloberl-retard®) 100 mg per day in capsule form during 15 days. Group II included 20 people who had received intramuscular injections of meloxicam 15 mg (1.5 ml) once a day during 5 days, followed by taking the drug in tablet form of 7.5 mg twice a day during 15 days.

At the screening all patients underwent a general clinical examination, anthropometric measurements (height, body weight and BMI calculation), assessment of pain syndrome, functional state of knee joints and general well-being.

Severity of the pain syndrome was assessed using the four-component Visual Analogue Scale (VAS) and the subscale of pain of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), stiffness according to the corresponding subscale of the WOMAC index, the functional state of knee joints according to the daily activity subscale of WOMAC, the Lequesne index and by conducting functional tests: «3 meter (sec)», «4 meter (sec)», «15 meter (sec)», «6-minute test (m)» and «sit to stand» test before the start of the therapy, on the 5th and 20th day of the treatment. The dynamics of pain reduction was evaluated in accordance with VAS daily during 1-5 days of the treatment. The assessment of tolerability and safety was studied by the method of controlling of undesirable phenomena and adverse reactions on the basis of subjective symptoms and feelings of the patient and objective data obtained by the researcher during the examination.

Statistical analysis was performed using the Statistica 10.0 program. The normality of the distribution of the obtained results was determined by the Shapiro-Wilk test. The results of the statistical analysis are presented as M ± SD, where M is the average value, SD is the standard deviation. The differences of the indices were considered reliable under the condition of p < 0.05. For the statistical analysis, the Student’s t test for related and independent samples and the test of Kruskal-Wallis were used in the case of non-parametric data distribution.

Results

The patients of both groups did not differ among themselves in terms of age, anthropometric data, and initial level of pain in knee joints (Table 1).
During the treatment, patients of both groups have demonstrated a significant decrease in the intensity of pain according to VAS compared to the initial data on the 5th and 20th day of the treatment ($p < 0.01$). However, there were no significant differences in the reduction of pain intensity according to VAS between the groups ($p = 0.36$ and $p = 0.67$ on the 5th and 20th day of the treatment). The number of the patients who had the VAS score improved > 50% on the 20th day of the treatment was 17 in group I and 13 in group II. These differences were not statistically significant ($p = 0.23$), which indicates about the high effectiveness of both drugs for the patients with knee OA.

Among the patients of both groups, a significant decrease in pain, stiffness and limitation of daily activities according to WOMAC subscales was also found compared to the initial level on the 5th and 20th day of the treatment. Thus, after 5 days of the treatment in group I, pain intensity decreased from $46.8 \pm 8.9$ to $26.2 \pm 14.1$ mm ($t = 6.1, p < 0.00001$) and from $49.9 \pm 14.4$ to $35.7 \pm 13.6$ mm ($t = 7.8, p < 0.00001$) in group II. In patients who received diclofenac sodium, the intensity of the pain syndrome after 5 days of the treatment was probably lower ($t = 2.8, p < 0.004$) than in group II. After completing the full course of the treatment, pain decreased from $46.8 \pm 8.9$ to $19.2 \pm 14.3$ mm ($t = 7.1, p < 0.00001$) in patients of group I and from $49.9 \pm 14.4$ to $21.5 \pm 14.1$ mm, respectively ($t = 6.9, p < 0.00001$), in patients of group II (Fig. 1).

The results of the study also had demonstrated a significant decrease in stiffness in accordance with data of WOMAC after 5 days of the treatment in group I from $53.1 \pm 23.7$ to $34.6 \pm 22.6$ mm ($t = 3.8, p < 0.001$) and from $57.8 \pm 20.1$ to $36.7 \pm 21.8$ mm ($t = 6.4, p < 0.0001$) in group II. After the completion of the full course of the treatment, stiffness index according to the WOMAC scale decreased from $53.1 \pm 23.7$ to $25.7 \pm 21.4$ mm ($t = 5.6, p < 0.0001$) in the patients of group I and from $57.8 \pm 20.1$ to $25.5 \pm 19.0$ mm ($t = 7.8, p < 0.0001$) in the subjects of group II.

Limitation of daily activities associated with knee OA decreased on the 5th day of the treatment with diclofenac sodium injections from $45.7 \pm 15.6$ to $33.1 \pm 17.7$ mm ($t = 4.2, p < 0.001$), and in the group of the patients, who received meloxicam, that is, $50.1 \pm 19.1$ to $23.3 \pm 17.7$ mm, respectively ($t = 5.8, p < 0.00001$) and from $50.1 \pm 19.1$ to $23.3 \pm 17.7$ mm, respectively, in the patients of the II group ($t = 6.9, p < 0.0001$).

Additionally, a faster decrease of the intensity of the pain syndrome of knee joints was registered among the patients who had received injections of the diclofenac drug. Thus, the level of pain according to the VAS on the 2nd and 3rd day of the treatment was probably lower in group I compared to the indices of group II ($p = 0.003$ and $p = 0.03$, respectively) (Fig. 2).

According to the results of the evaluation of the algofunctional Lequesne index, a significant improvement was found among the patients of both groups against the background of the treatment. Thus, in group I, a significant improvement for $22.5\%$ on the 5th day of the treatment ($p < 0.01$) and $31.4\%$ ($p < 0.01$) on the 20th day was found. In group II, the corresponding indices on the 5th and 20th day decreased by $16.2\%$ ($p < 0.01$) and by $24.2\%$ ($p < 0.01$), respectively. There were no significant differences in indices in the groups I and II after 5 and 20 days of the treatment.

A significant improvement in functional performance using the “3-meter”, “4-meter”, “15-meter”, “6-minute test” and the “sit-to-stand” tests was found in both groups on the 5th and 20th days of the treatment. Thus, in group I, the duration of the “3-meter test” on the 5th day of the treatment significantly improved by $9.7\%$ ($p < 0.01$) and by $12.0\%$ on the 20th day ($p < 0.01$). In group II, the improvement in its performance was $5.2\%$ ($p < 0.01$) and $11.3\%$ ($p < 0.01$), respectively, on the 5th and 20th day of the treatment.

Improvement of the indices of the “6-minute test” in group I amounted to $2.9\%$ ($p < 0.01$) after the course of injections and by $3.4\%$ – after the completion of the full course of the treatment ($p < 0.01$) and by $0.9\%$ ($p < 0.01$) and $1.4\%$ ($p < 0.01$) in group II.

In accordance with the results of the “sit-to-stand” test, it was found that in group I, the duration of its performance on the 5th day of the treatment significantly decreased by $11.5\%$ ($p < 0.01$) and by $10.8\%$ ($p < 0.01$) on the 20th day. In group II, test performance index improved by $8.6\%$ ($p < 0.01$) and $13.7\%$ ($p < 0.01$), respectively, on the 5th and 20th day of the treatment.

Any adverse events or side effects, which would require withdrawal or change of the dose of the studied drugs or the use of additional treatment, had not been registered in both groups during the entire study.

### Table 1. Characteristics of the examined patients

<table>
<thead>
<tr>
<th>Indices</th>
<th>Group I</th>
<th>Group II</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
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<td>66.0 ± 7.6</td>
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<tr>
<td>Body mass, kg</td>
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<td>80.8 ± 12.7</td>
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<tr>
<td>Height, cm</td>
<td>161.1 ± 7.9</td>
<td>162.3 ± 5.4</td>
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<td>0.84</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>30.7 ± 4.3</td>
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<td>0.88</td>
</tr>
<tr>
<td>VAS, units</td>
<td>5.7 ± 1.2</td>
<td>5.9 ± 1.6</td>
<td>0.5</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Note. t — Differences in the indices had been evaluated with the help of Student’s test.
Discussion

All over the world, diclofenac sodium remains the drug of choice in the presence of the vast majority of pain syndromes, at the same time; it also has antipyretic and anti-inflammatory effects. Like most of NSAIDs, diclofenac reduces the concentration of proinflammatory and nociceptive prostaglandins in synovial fluid and blood by inhibiting their synthesis. Diclofenac is often used as a comparator in randomized controlled trials as for the evaluation of the effectiveness of NSAIDs in the presence of OA. The results of clinical trials indicate its high efficiency, which is not inferior to newer molecules of NSAIDs [6].

Most often, diclofenac is prescribed in oral form, but also local, intravenous, intramuscular, subcutaneous and rectal forms of administration are often used. Parenteral forms are in priority if it is necessary to start quickly analgesia of the patient [9]. Intramuscular administration provides higher bioavailability and speed of the development of the therapeutic effect of the drug compared to the local rectal or oral form [10].

According to the literature, the drugs of diclofenac and meloxicam showed the most pronounced effect as for reducing the intensity of pain in accordance with VAS [11]. In a study conducted by Hosie J. and co-authors, in which three hundred and thirty-six patients had been examined who received oral meloxicam 7.5 mg 1 time per day or diclofenac 100 mg 1 time per day during 6 months, both drugs had demonstrated a high level of efficacy. However, the authors did not obtain reliable differences between the groups of the treatment regarding the reduction of knee joints pain during movement and at rest, the overall assessment of the effectiveness of the treatment, or the assessment of the quality of life at the end of the treatment [12]. According to the results of our study, a decrease in pain intensity according to VAS on the 5th day of the treatment was also found in group I by 33.3 % and in group II by 30.1 % (p < 0.01 for both groups), and on the 20th day in 57.9 and 56.6 %, respectively, in groups I and II (p < 0.01 for both groups), however, no significant differences in indices between the groups were obtained (p = 0.36 and p = 0.67 on the 5th and 20th days of the treatment).

According to the results of a meta-analysis, which included 192 studies with the participation of 102,829 subjects, where the effectiveness and safety of 90 active schemes
of the treatment of NSAIDs had been compared, opioids and paracetamol with oral placebo, the most effective drugs for reducing pain in the patients with OA of knee and hip joints were found to be diclofenac at a dose 150 mg/d and etoricoxib – 60 mg/d [13].

According to the data of another meta-analysis in which the effectiveness of different schemes of NSAID treatment based on the results of 8,973 published studies had been compared, among which 76 were randomized trials with a total quantity of 58,451 patients, diclofenac at a dose of 150 mg/d was the most effective in terms of reducing pain intensity and restoring physical function. The effectiveness of the treatment varied depending on the active substance of the NSAID and its dose. While paracetamol showed a minimal effect on the severity of pain syndrome under use of different doses that corresponded to a difference of 4.5 mm per 100 mm of VAS diclofenac sodium at a dose of 150 mg/d had demonstrated an effect corresponding to a difference of 14 mm on the scale of pain according to VAS. This rate was 1.5 times greater than the minimum clinically important difference for the treatment of chronic pain. The results of this meta-analysis also testify that a typical OA patient has a 100 % probability of minimal clinically important improvement when receiving diclofenac sodium 150 mg/d, etoricoxib 60 mg/d, or rofecoxib 25 mg/d [14]. According to the results of our study, the reduction of pain on the 20th day of the treatment was 33 mm in groups I and II (p<0.01 for both groups).

According to the data of various authors, the intensity of the pain syndrome according to the WOMAC pain subscale among the patients who use diclofenac sodium decreases to 88.9 % after 4 weeks of the treatment. After 4 weeks of the treatment, the VAS pain index decreases from the initial level to 79.3 %, the stiffness index to 78.1 %, and the quality of life index to 76.5 % [15]. In accordance with the results of our study, on the 20th day of the treatment with diclofenac sodium, the WOMAC pain index decreased by 55.5 % (p < 0.01), stiffness – by 51.5 % (p < 0.01), and quality of life – by 42.6 %.

The limitation of this study is the research design (it was conducted in one center), the inclusion of only women at the age of 50-75 years old, and a short observation period (20 days).

Conclusions

The use of diclofenac sodium and meloxicam against the background of complex non-drug treatment of knee OA is effective and safe, however, in the case of using diclofenac sodium, analgesia occurs faster, which is manifested by a significantly more pronounced decrease of the intensity of the pain syndrome already on the 2-nd and 3-rd day of the treatment.

References

Порівняльна оцінка ефективності пацієнтів із симптоматичним остеоартритом колінних суглобів


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Authors’ contribution. Pavelka K. — conception and design of the study; Bystrytska M.A. — statistical processing, writing the text; Musienko A.S. — collection and processing of the material, writing the text; Zaverukha S.N. — analysis of the literature resources, collection and processing of the material, writing the text; Grygor'ieva N.V. — analysis of the data obtained, correction of the text; Tkachuk A.A. — processing of the primary material; Solonenko T.Yu. — processing of the primary material.
старі віком 50–75 років із симптоматичним ОА КС, які були розподілені на 2 групи: група І — 20 осіб, які отримували диклофенак натрію; група ІІ — 20 хворих, які отримували мелоксикам. На кожному візиті проводили оцінку інтенсивності болю, як асоціаційніх засобів, так і функціонального стану КС за допомогою шкали WOMAC, чотирьохскладової візуально-аналогової шкали (WASH), індексу Лекена та шляхом проведення функціональних тестів. Безпечність лікарських засобів визначали за частотою побічних явищ.

Результати. Пацієнти обох груп не відрізнялися за віком та початковим рівнем болю за ВАШ. На тлі лікування пацієнти обох груп продемонстрували значне зниження інтенсивності болю за ВАШ на 5-ту та 20-ту добу лікування (р < 0,01) без вірогідних відмінностей між групами, але у хворих групи І рівень болю за ВАШ на 2-гу та 3-тю добу лікування був вірогідно нижчим порівняно з показниками групи ІІ (р = 0,003 та р = 0,03 відповідно). Також у пацієнтів обох груп виявлено вірогідне зменшення показників болю, скутості та обмеження повсякденного активності за субшкалами WOMAC на 5-ту та 20-ту добу лікування, проте у групі І інтенсивність болю була вірогідно меншою (t = 2,8, р < 0,004), ніж у групі ІІ.

Висновки. Застосування диклофенаку натрію та мелоксикаму на тлі комплексного немедикаментозного лікування ОА КС є ефективним та безпечним, проте у разі застосування диклофенаку натрію знеболювальна дія проявляється вірогідно більш вірогідним зниженням інтенсивності болю через 5–7 діб лікування у групі І. Ключові слова: остеоартрит колінних суглобів; диклофенак натрію; мелоксикам