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EFFICACY OF USING MELOXICAM IN THE TREATMENT OF OSTEOARTHRITIS IN PATIENTS WITH COMORBID PATHOLOGY

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INTRODUCTION

Osteoarthritis (OA) is one of the most common diseases and occurs in more than 10–20% of the world's population and correlates with age[1,2,3].

The prevalence of OA in Ukraine is 2515.7 per 100 thousand population, the incidence is 527.0 per 100 thousand, and the primary disability among the working population is 0.7 per 10 thousand people[4].

It is also known that the older a person is, the more prone he is to diseases of organs and systems. Old age is not a disease or a diagnosis. The physiological process of aging of the human body begins to be observed from 40–50 years. Violation of the structure and function of all organs and systems is intensifying. Thus, the aging of the body contributes to the emergence and accumulation of diseases[5,6,7].

According to a report by the World Health Organization (WHO) on the social consequences of the disease, gonarthrosis ranks fourth among the causes of disability among women and eighth among men. Research

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data show that OA is one of the main causes of temporary and permanent disability[8].

People who are overweight, ie obese, mostly suffer from knee joints due to their chronic overload. Other important risk factors for OA are also discussed immune mechanisms of circulatory disorders in joint tissues, hereditary predisposition when congenital malformations of the skeleton are possible, weakness of dryligament and other disorders that lead to change congruence of joint surfaces and the development of OA[9,10].

It is interesting that the results of general clinical blood and urine tests for OA remain virtually unchanged. Only in severe secondary synovitis can the erythrocyte sedimentation rate (ESR) increase moderately to 11-23 mm / h and the protein concentration increases in the acute phase of inflammation[11,12,13].

Non-steroidal anti-inflammatory drugs (NSAIDs) rank first in the world in terms of scale and frequency of use. More than 30 million people in the world take NSAIDs over the age of 60 – more than 40%. At the same time, 2/3 of them are without a doctor's recommendation and control[14,15].

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The modern approach to treatment is based on the principles of evidence-based medicine, the implementation of standards, protocols and guidelines, based on multicenter international research[16,17].

Given that an elderly patient with OA may usually have concomitant cardiovascular disease (CVD) at the same time, the physician must be aware of the potential risks of the prescribed therapy. Against the background of comorbidity, excessive administration of drugs without taking into account the peculiarities of their interaction and can lead to a sharp increase in the likelihood of adverse effects of therapy and deterioration of the patient's condition[18,19].

Comorbidity in OA is observed in almost 94% of patients – almost 5 times more often than in the general population[20]. According to recent studies, OA is most common in patients with hypertension (GC) and other CVD, which occur in more than 50% of patients with OA.

A special role in the pathogenesis of OA belongs to nitric oxide (NO), which is able to inhibit the synthesis of cartilage macromolecules, increase the activity of inflammatory reactions[21].

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1. Analysis of the effectiveness of the use of meloxicam according to the visual-analog scale (VAS) for patients with osteoarthritis of the knee

Pain is considered one of the main diagnostic criteria for the effectiveness of treatment of osteoarthritis. However, in clinical practice, the effect of drugs with long-term use in the treatment of patients with osteoarthritis, for example, as in our study, such as selective nonsteroidal anti-inflammatory (NSAID) drug (in our study – meloxicami). Given the above, further study of the safety and efficacy of a new generation of NSAID drugs is an urgent scientific problem that needs to be addressed.

To conduct the above studies, patients were divided into three groups:. Group 1. This group included patients with osteoarthritis of the knee joints.

Group 2. This group included patients with osteoarthritis in combination with hypertension.

Group 3. This group included patients with osteoarthritis in combination with hypertension and gastropathy.

Table 1

Dynamics of indicators (VAS) of the studied groups of patients under the influence of treatment

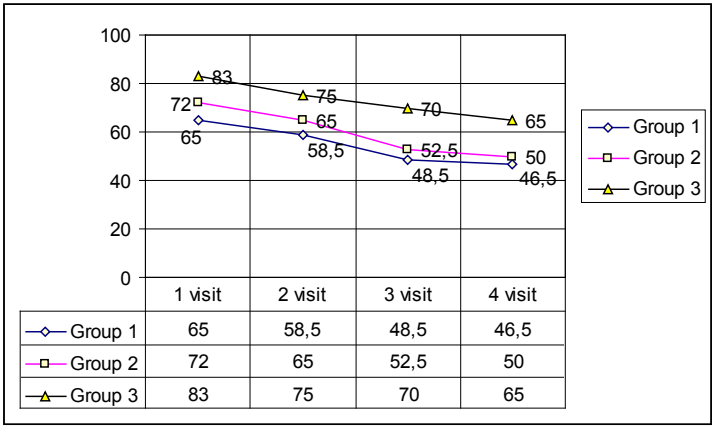
Groups / Visits	Group 1 n = 30		Group 2 n = 30		Group 3 n = 30		p- level of significance
Indicators, (VAS) mm	Me	IQR	Me	IQR	Me	IQR	
	1		2		3		
1 visit (before treatment)	65,0	55,0 - 70,0	72,0	65,0 - 75,0	83,0	75,0-85,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$
2 visit (in 4 months)	58,5	49,0-63,0	65,0	57,0-70,0	75,0	65,0-77,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$
3 visit (in 8 months)	48,5	41,0-56,0	52,5	52,5-60,0	70,0	60,0-73,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$
4 visit (in 12 months)	46,5	65,0 - 53,0	50,0	45,0 - 57,0	65,0	50,0-67,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$

In all the studied groups on the background of the treatment there was a positive dynamics of the joint syndrome (Table 1).

Under the influence of treatment with meloxicami (melbeci) in all patients, both isolated osteoarthritis of the knee and combined with hypertension and in the group with osteoarthritis combined with hypertension and aggravated by gastropathy, there were positive changes in joint status.

During treatment, the number of patients with high pain intensity probably decreased in all 3 groups, in some patients the pain was transformed into mild..

After 12 months of treatment, the analgesic effect was more significant, there was a reduction in the number of patients with high pain intensity in the 1st group (by%), in the 2nd group (by%), in the 3rd group (by%). As a result of the study, patients noted a reduction in pain in CS, improvement in general well-being and QOL. During the analysis of pain intensity for VAS, a significant decrease in indicators was found (Table 1). After 12 months, VAS indicators decreased by 11% in group 1, 13% in group 2, 12% in group 3.



	1 visit	2 visit	3 visit	4 visit
Group 1	65	58,5	48,5	46,5
Group 2	72	65	52,5	50
Group 3	83	75	70	65

Fig. 1. The dynamics of the visual analog scale (VAS)of pain according to the assessment of patients in patients of the studied groups under the influence of treatment

As can be seen from Figure 1. the best indicators of VAS results were found in patients with radiological stage 1 according to Kelgen – Lourence, and slightly worse with stage 11. These results indicate that

meloxicami is more effective in the early stages of treatment of osteoarthritis of the knee.

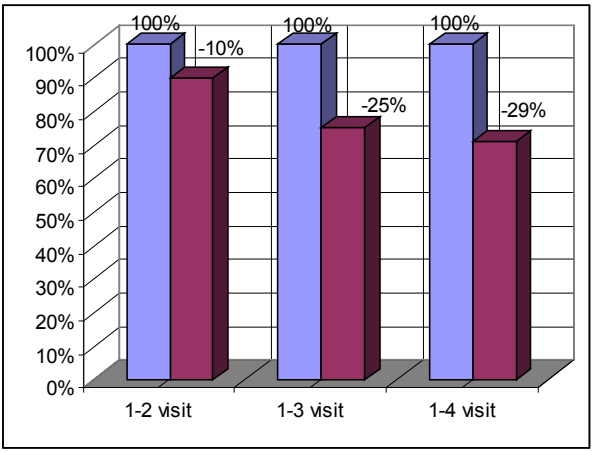


Fig. 2. Comparison of the dynamics indicators in the visual-analogue scale of pain until group (Group 1) for sale 12 months($p < 0.05$)

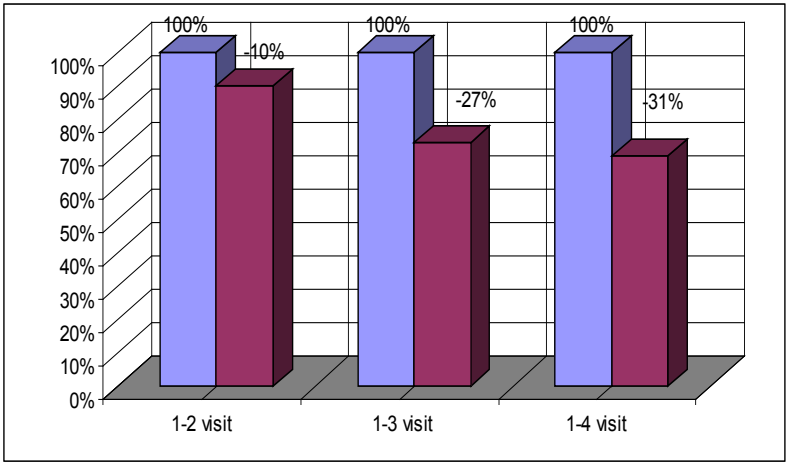


Fig. 3. Comparison of the dynamics of the visual-analog scale of pain of the study patients (Group 2) during 12 months of treatment

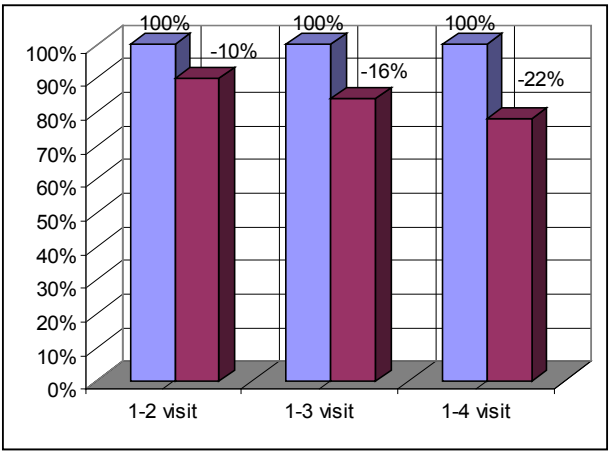


Fig. 4. Comparison of the dynamics of the visual-analog scale of pain of the studied patients (Group 3) during 12 months of treatment (p <0.05)

2. Analysis according to the algae functional index of Leken

Persistent chronic osteoarthritis of the knee requires long-term and sometimes continuous use of NSAID, which causes a high risk of side effects. Risk factors are the presence of pathology of the digestive tract, in the anamnesis, taking high doses of NSAID, antiplatelet therapy. Particularly high risk of side effects – in the elderly, who make up the main contingent of patients with osteoarthritis of the knee preparation. It should be noted that for 12 months in all 3 groups of patients side effects when taking meloxicam were not observed, which determines a sufficient profile of safety and tolerability of the drug.

The obtained data confirm the feasibility of using the drug meloxicam (melbeck) in patients with OA CS, both in an isolated course and in the presence of comorbid pathology. Assessing the severity of gonarthrosis using the alkaline functional index of Lecken, we found that during treatment significantly decreased by 11% in group 1, 13% in group 2, 12% in group 3. Also from these results we can conclude that the effectiveness of meloxicam is higher in patients with gonarthrosis with I radiological stage than with II. In the Ist group at the end of the study (12 months) there was a significant decrease in the Leken index, at the same time in the 2nd and 3rd groups there was only a tendency to decrease.

Table 2

Dynamics of changes in the indicators of algofunctional Leken index of the studied group of patients with osteoarthritis under the influence of treatment

Groups / Visits	Group 1 n = 30		Group 2 n = 30		Group 3 n = 30		p-level of significance
Leken index, points	**Me**	**IQR**	**Me**	**IQR**	**Me**	**IQR**	
	1		2		3		
1 visit (before treatment)	6,0	5,0 – 7,0	7,0	7,0 – 8,0	9,0	8,0 – 11,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$
2 visit (in 4 months)	5,0	4,0 – 6,0	6,0	6,0 – 7,0	8,0	7,0 – 10,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$
3 visit (in 8 months)	4,0	3,0 – 5,0	5,0	4,0 – 6,0	6,0	5,0 – 7,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$ $p_{2-3}<0.05$
4 visit (in 12 months)	3,0	2,0 – 5,0	4,0	3,0 – 5,0	5,0	4,0 – 7,0	$p_{1-2}<0.05$ $p_{1-3}<0.05$

During the observation period in all 3 groups there were no significant changes in the indicators characterizing the function of the liver and kidneys, as well as those that would require a reduction in the dose of drugs, or their cancellation.

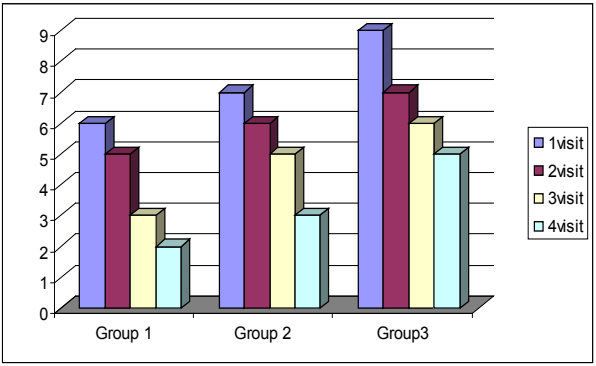


Fig. 5. Dynamics of algofunctional Leken index in the studied groups of patients under the influence of treatment

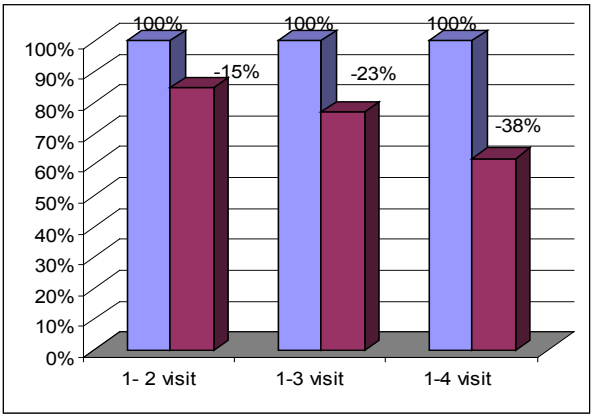


Fig. 6. Dynamics of changes in the alkefunctional Leken index of a group of patients (Group 1) under the influence of treatment

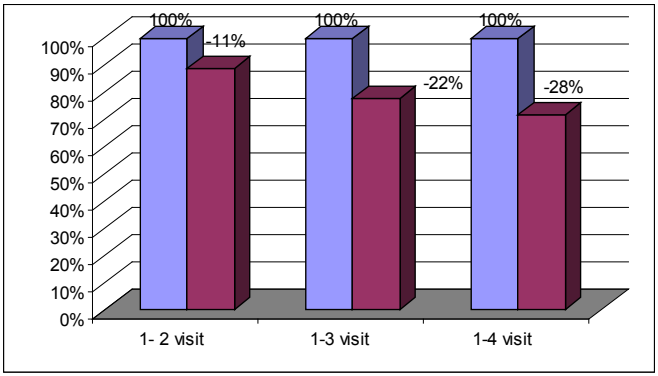


Fig. 7. Dynamics of changes in the alkefunctional Leken index of a group of patients (Group 2) under the influence of treatment

The study did not reveal negative dynamics of such laboratory parameters as hemoglobin, erythrocytes, total bilirubini, ALT, AST, creatinini, total proteini, glucose, ESR, which in all patients included in the study were within normal limits.

All patients according to the design of this study were conducted: general clinical, laboratory (general blood test, general urine test, glucose blood, ALT.

Table 3

Dynamics of biochemical parameters of the study groups of patients with osteoarthritis (Group 1) during treatme

Indicators, units	Before treatment		After treatment		p-level significance,
	Me	IQR	Me	IQR	
	1		2		
Hb, g / l	139	127,8-152,90	140	124,60 –154,00	$p_{1-2}<0.05$
Er, 10^{12} /l	4,4	4,05 – 4,84	4,8	4,2 7 – 5,28	$p_{1-2}<0.05$
ESR mm / h	4	3 -5	5	4,45 – 5,50	$p_{1-2}<0.05$
Blood glucose, mmol / l	4,02	3,70 – 4,42	3,5	3,12 – 3,85	$p_{1-2}<0.05$
ALT, units / l	0,19	0,17 – 0,21	0,2	0,18 – 0,22	$p_{1-2}<0.05$
AST, units / l	0,21	0,19 – 0,24	0,22	0,20 – 0,24	$p_{1-2}<0.05$
Bilirubini general. μmol / l	11,06	9,95 – 12,50	11,1	10,10 – 12,10	$p_{1-2}<0.05$
Creatininш, μmol / l	76.78	69,10 – 86,76	77,21	70,26 – 84,16	$p_{1-2}<0.05$
Total protein, g / l	69,51	62,56 – 78,55	68,81	62,62 – 75,00	$p_{1-2}<0.05$

Table 4

The results of biochemical parameters of the study of groups of patients with osteoarthritis in combination with hypertension (Group 2) during treatment with osteoarthritis in combination with hypertension and gastropathy (Group 3) during treatment

Indicators, units	Before treatment		After treatment		p-level significance,
	Me	IQR	Me	IQR	
	1		2		
Hb, g / l	139	127,8-152,90	140	124,60 –154,00	$p_{1-2}<0.05$
Er, 10^{12} /l	4,4	4,05 – 4,84	4,8	4,2 7 – 5,28	$p_{1-2}<0.05$
ESR mm / h	4	3-5	5	4,45 – 5,50	$p_{1-2}<0.05$
Blood glucose, mmol / l	4,02	3,70 – 4,42	3,5	3,12 – 3,85	$p_{1-2}<0.05$
ALT, units / l	0,19	0,17 – 0,21	0,2	0,18 – 0,22	$p_{1-2}<0.05$
AST, units / l	0,21	0,19 – 0,24	0,22	0,20 – 0,24	$p_{1-2}<0.05$

Table 4 (continuance)

Bilirubini general. μmol / l	11,06	9,95 – 12,50	11,1	10,10 – 12,10	p_{1-2} <0.05
Creatininш, μmol / l	76.78	69,10 – 86,76	77,21	70,26 – 84,16	p_{1-2} <0.05
Total protein, g / l	69,51	62,56 – 78,55	68,81	62,62 – 75,00	p_{1-2} <0.05

Table 5

The results of biochemical parameters of the study group of patients

Indicators, units	**Before treatment**		**After treatment**		**p-level significance,**
	Me	**IQR**	**Me**	**IQR**	
	1		2		
Hb, g / l	140	127,3 – 154,0	141	129,7 – 154,96	p_{1-2} <0.05
Er, 10^{12} /l	4,3	3,91 – 4,73	4,0	3,68 – 4,40	p_{1-2} <0.05
ESR mm / h	8	7,28 – 8,80	7	6,44 – 7,69	p_{1-2} <0.05
Blood glucose, mmol / l	5,48	4,99 – 6,03	4,98	4,58 – 5,47	p_{1-2} <0.05
ALT, units / l	0,22	0,20 – 0,25	0,2	0,18 – 0,22	p_{1-2}<0.05
AST, units / l	0.25	0,23 – 0,28	0,21	0,19 – 0,23	p_{1-2} <0.05
Bilirubini general. μmol / l	13.85	12,47 – 15,65	14,1	12,41 – 15,51	p_{1-2} <0.05
Creatininш, μmol / l	96,75	87,0 -109,33	92,14	81,08 – 101,35	p_{1-2} <0.05
Total protein, g / l	73,25	65,93 – 82,77	74,12	65,23 – 81,53	p_{1-2} <0.05

ACT, total bilirubin, total protein, creatine, lipid blood spectrum, C-reactive protein); anthropometric; instrumental. The scientific novelty of the study will be that for the first time: the peculiarities of the comorbid course of OA and GC and the degree of SSR, which is incredibly important in determining strategy and tactics treatment, and is an indication for more aggressive prevention of those GC treatment; the functional state of the knee joints in the conditions of OA combination was investigated and GC using the Leken questionnaire

for knee joints; visual – analog scale (YOUR) to study the level of pain; the state of cardiac hemodynamics and DMAT, and their changes under the influence of treatment, in the conditions of a comorbid course of OA and GC is estimated. The clinical efficacy and safety of the drugs used in the study (selective NSAID meloxicam and antihypertensive drug Difors), their effect on QOL in patients with OA in combination with GC before and after treatment with the SF – 36 questionnaire, which would be the basis for substantiation its improvement and registration of the invention on a utility model (Method of complex treatment of osteoarthritis in patients with arterial hypertension: Pat. 135690 Ukraine: BETWEEN A61K 31/00, A61R 19/02. № u 2019 01439; application 13.02.2019; publ. 10.07. 2019. Bull. № 13.Inventors: Kuznetsova Lyubov Pylypivna UA Alipova Olena Yevhenivna UA Bondar Maria Vadymivna UA.

3. Relationship of C-reactive protein with inflammatory processes of the studied groups of animals during meloxicam treatment

In the modern medical literature (in articles that report the results of research) much attention is paid to the role of C-reactive protein, which is argued by convincing evidence of the important role of inflammation in the pathogenesis of osteoarthritis. However, individual, personalized approaches to the management of patients with osteoarthritis remain insufficiently developed. Immune disorders are of great importance in the development of osteoarthritis. The destruction of cartilage proteoglycans is accompanied by the development of immune reactions of cellular and humoral type.

Thus, the continuation of scientific research on the assessment of individual clinical and instrumental features of osteoarthritis of the knee joints and personalized tactics of the patient is quite relevant because it allows to justify individual treatment tactics in patients with osteoarthritis, as with isolated course, so with comorbid pathology

The most sensitive objective indicator of the systemic inflammatory process is C-reactin protein (PSP).

Elevated PSA levels were found in the examined groups of patients. This fact indicates a significant role of inflammatory changes in the pathogenesis of osteoarthritis, which coincides with the data of scientific sources.

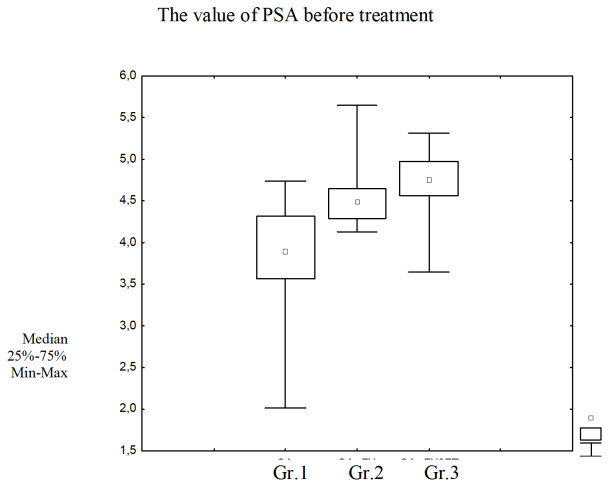


Fig. 8. The level of C-protein in the studied groups of patients before treatment

Normalization of PSA levels on the background of rescribed therapy occurred in all groups of patients. The tendency to a more pronounced dynamics of PSA reduction among patients of group 1, while in groups 2 and 3.

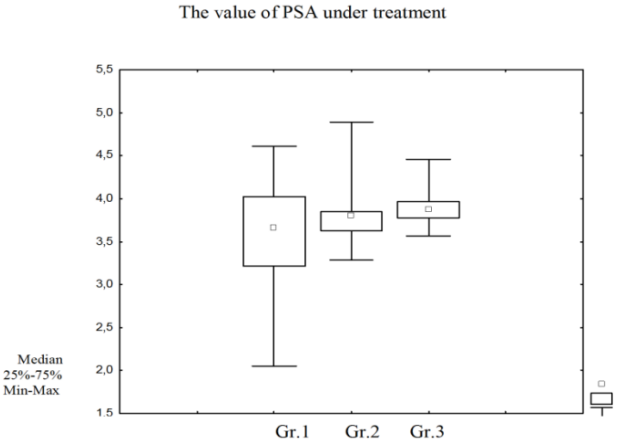


Fig. 9. The level of C-protein in the studied groups of patients under

Meloxicam showed a pronounced anti-inflammatory effect according to the PSA, as one of the main indicators of the severity of the inflammatory process. Against the background of treatment with meloxicam in most patients decreased the need for NSAIDs, which is one of the indicators of the effectiveness of treatment of osteoarthritis. Long-term use of the drug is pathogenetically justified, effective and safe.

This combination of degenerative and proliferative changes, which is more common in the elderly, requires timely diagnosis and targeted treatment with effective drugs, which in turn prevents the disability and improvement of QOL in patients with osteoarthritis.

The dynamics of reducing the intensity of pain, markers of inflammation, a positive subjective assessment of the effectiveness of treatment, were more pronounced among patients with isolated osteoarthritis of the knee joints (Group 1) than in patients from the group of patients with osteoarthritis in combination with hypertension (Group 2) and patients with osteoarthritis in combination with hypertension and gastropathy (Group 3) associated with the presence of comorbid pathology, its aggravating effect on the disease.

A direct correlation was established between the determination of pain by VAS and the level of PSA in patients of Group 1 after treatment ($R=0.59$, $p<0.05$).

There is a direct correlation between the determination of pain by VAS and the level of PSA in patients of Group 2 after treatment ($R = 0.51$, $p<0.05$).

There is a direct correlation between the determination of pain by VAS and the level of PSA in patients of Group 3 after treatment ($R= 0,29$, $p < 0,05$).

In patients at increased risk of gastrointestinal disease with the use of selective NSAIDs – (in our study it is meloxicam) selective NSAIDs should be prescribed in combination with the addition of a proton pump inhibitor. This combination is useful and reduces the risk in these cases. The association of meloxicam in our study with increased cardiovascular risk is a complex issue. We were concerned about a direct indirect imbalance of prostanoids, which may be indirect and will be associated with elevated blood pressure.

But during our study, the prohypertensive effect of meloxicam was not observed. But this must always be kept in mind by physicians, using personalized approaches to the management of patients with osteoarthritis of the knee with comorbid pathology.

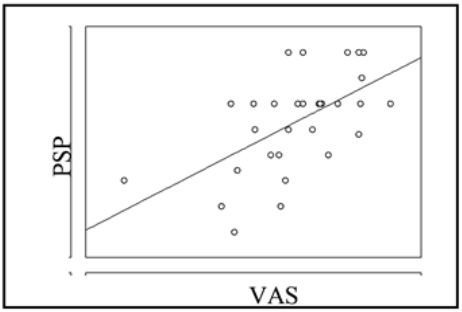


Fig. 10. Correlation between the definition of pain by VSA and PSA level. in patients of Group 1 after treatment

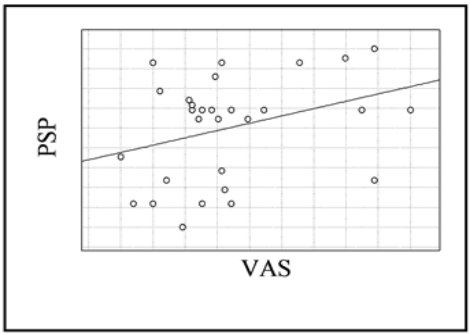


Fig. 11. Correlation between the definition of pain by VAS and PSA level in patients of Group 2 after treatment

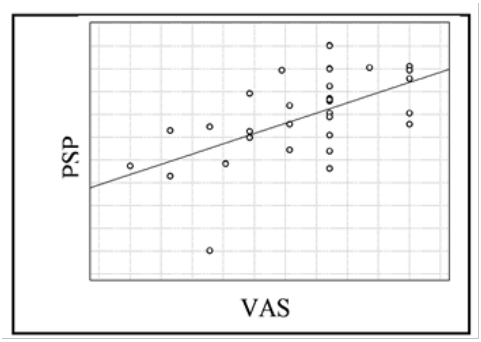


Fig. 12. Correlation between the definition of pain by VAS and PSA level in patients of Group 3 after treatment

CONCLUSIONS

1. The study is devoted to improving the diagnosis and treatment of patients with osteoarthritis of the knee joints stage I-II in combination with hypertension stage II 2–3 degrees at the stage of providing medical care by family doctors in primary health care facilities.

2. This is embodied by personalized optimization of therapy (by attracting safe and effective long-term use of selective nonsteroidal anti-inflammatory drugs (NSAIDs), a fixed combination of antihypertensive drugs). This reduces gastrointestinal and cardiovascular risks, increases patients' adherence to treatment and their quality of life.

3. Treatment with meloxicami in patients with OA of the knee joints with a comorbid course confirmed the high effectiveness of the drug. The use of meloxicami in therapy helps to reduce the severity of pain, improve the functional state of the musculoskeletal system.

4. The results also indicate good tolerability and safety of meloxicam, which is the basis for the widespread use of the drug in the practice of family medicine as a selective NSAID.

5. Long-term meloxicam therapy is associated with a risk of side effects that require treatment monitoring.

SUMMARY

The modern approach to the treatment of diseases is based on the principles of evidence-based medicine, the implementation of standards, protocols and guidelines, based on multicenter research. But this applies only to certain nosological forms, or even some symptoms of the disease (VM Kovalenko, 2019; BV Zavodovsky, 2015). This approach does not involve clinical situations involving a combination of several diseases that often occur from middle age. Today, this situation is defined as comorbidity.

Prominent American physician-epidemiologist AI Epizin, who first proposed this term, considered comorbidity to have an additional clinical picture, regardless of the underlying disease, which is always the case. different from the main. That is, comorbidity is not just a combination of several diseases, but also the presence of new mechanisms of disease development, complications and course, uncharacteristic of the underlying disease, as well as a significant impact on quality and life expectancy of patients (Bereznyakov IG, Korzh IV, 2012; Kozlyuk AS, 2014; Protsenko GO; Ivanova KA 2013, Suprun EV, 2013).

Osteoarthritis (OA) is the most common chronic joint disease, occurring in more than 10 to 20% of the world's population and correlating with age. The aging population around the world in recent years has led to an increase in the incidence of OA. A is characterized by pain, significant structural changes in the joints and functional disorders. Pain syndrome in this disease is the main reason for patients to seek medical help from a family doctor and causes not only significant temporary disability of young and middle-aged people, but also early disability.

The prevalence of GC in Ukraine, as in most European countries, currently reaches a third of the population and is an important medical and social problem that leads to most cardiovascular complications (CVD) (Kovalenko VM, 2019, Sirenko Yu.M., 2018; Lashkul ZV, 2014): development of heart failure (HF), myocardial infarction, fatal disorders of heart rhythm and conduction, chronic renal failure – (Amosova KM, 2019).

It is known that in patients with OA GC is more common than in the population. In combination with these diseases observed in 45-58% of the population. Both OA and GC occur mainly in older age groups. The combination of OA and GC causes not only a medical but also an important social problem. This is due to the wide prevalence of these diseases, the high risk of complications, the deterioration of the QOL of patients due to constant pain, as well as persistent disability.

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