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ПАЦИЕНТЫ С СЕРДЕЧНО-СОСУДИСТЫМИ ЗАБОЛЕВАНИЯМИ И ПРИЕМ НПВП: РЕАЛЬНАЯ КЛИНИЧЕСКАЯ ПРАКТИКА

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Patients with cardiovascular diseases and NSAIDs use: real clinical practice

Резюме

Цель — изучить частоту и особенности применения нестероидных противовоспалительных препаратов (НПВП) у пациентов с сердечно-сосудистыми заболеваниями, госпитализированных в отделения экстренной кардиологии. **Материалы и методы.** Обследовано 190 пациентов, госпитализированных в отделения экстренной кардиологии ГУЗ «Областная клиническая больница» г. Саратова с января по март 2020г. Исследование являлось непрерывным, анкетирование проводилось всем пациентам, госпитализированным в указанный период. В исследовании приняли участие 103 (54%) мужчины и 87 женщин, средний возраст пациентов составил 62,05 ± 11,11 года. Причиной госпитализации у большинства пациентов явилась острая коронарная патология — 116 (61%), у 34 (18%) пациентов — декомпенсация сердечной недостаточности, у 21 (11%) — различные нарушения ритма; у 15 (8%) — гипертонический криз на фоне неконтролируемой артериальной гипертензии, у 4 (2%) пациентов — тромбоэмболия легочной артерии. **Результаты.** В течение месяца перед госпитализацией НПВП по различным причинам принимали 92 (48%) пациента: 42 (46%) мужчины и 50 (54%) женщин. Средний возраст пациентов, принимавших НПВП, выше, чем у пациентов, не принимавших НПВП (63,98±11,62 года и 60,20±10,27 лет, соответственно, p=0,018). Среди пациентов, вынужденных принимать НПВП в течение последнего месяца, боль в суставах, как основную причину или одну из причин приема НПВП указали 43 (47%) пациента, головную боль — 40 (43%) пациентов, боль в спине — 30 (33%) больных. У 15 (16%) пациентов причиной приема НПВП явилась зубная боль, у 14 (15%) — боль в грудной клетке, у 11 (12%) больных — мышечно-скелетные боли. Несколько причин для приема НПВП отметили 40 (43%) пациентов (в основном, сочетание суставных болей и болей в спине). **Заключение.** Почти половина пациентов, госпитализированных в отделения экстренной кардиологии, в течение предшествующего месяца принимали НПВП. Большая часть пациентов вынуждена принимать НПВП часто, регулярно и продолжительно. Более трети обследованных пациентов использовали различные способы введения препаратов, в том числе неоправданно частое и длительное парентеральное применение или одновременное использование различных способов введения различных лекарственных препаратов.

Ключевые слова: *сердечно-сосудистые заболевания, нестероидные противовоспалительные препараты*

Конфликт интересов

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Abstract

Objective — to study the frequency and characteristics of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with cardiovascular diseases hospitalized in the emergency departments of cardiology. **Materials and methods**. Examined 190 patients hospitalized in the emergency cardiology departments of the State Healthcare Institution Regional Clinical Hospital of Saratov from January to March 2020. The study was continuous, a questionnaire was conducted for all patients hospitalized during the specified period. The study involved 103 (54%) men and 87 women, the average age of the patients was 62.05 ± 11.11 years. The reason for hospitalization in most patients was acute coronary pathology — 116 (61%) patients, 34 (18%) patients — decompensated heart failure, 21 (11%) patients — various rhythm disturbances; in 15 (8%) patients — hypertensive crisis against the background of uncontrolled arterial hypertension, in 4 (2%) patients — pulmonary embolism. **Results.** During the last month, 92 (48%) patients took NSAIDs for various reasons: 42 men (46%) and 50 women (54%). The average age of patients taking NSAIDs is higher than that of patients who did not take NSAIDs (63.98 ± 11.62 years and 60.20 ± 10.27 years, respectively, p = 0.018). Among patients forced to take NSAIDs over the past month, joint pain — 43 (47%) patients, headache — 40 (43%) patients, back pain — 30 (33%) were indicated as the main cause or one of the reasons sick. In 15 (16%) patients, the reason for taking NSAIDs was toothache, in 14 (15%) patients — chest pain, musculoskeletal pain — in 11 patients (12%). Several reasons for taking NSAIDs were indicated by 40 (43%) patients, the majority — a combination of joint pain and back pain. **Conclusion**. Almost half of patients admitted to emergency cardiology departments had taken NSAIDs in the previous month. Most patients have to take NSAIDs often, regularly, for a long time. More than a third of the examined patients used various methods of drug administration, including unreasonably frequent and prolonged parenteral use or the simultaneous use of various methods of administration of various drugs.

Key words: *cardiovascular diseases, nonsteroidal anti-inflammatory drugs*

Conflict of interests

The authors declare no conflict of interests

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FC — functional class, GIT — gastrointestinal tract, GFR — glomerular filtration rate, IHD — ischemic heart disease, NSAIDs — non-steroidal anti-inflammatory drugs

Introduction

Today, there are many publications on the rational use of non-steroidal anti-inflammatory drugs (NSAIDs) and possible risks of adverse events in patients with cardiovascular diseases while taking NSAIDs [1–4]. The possible increase of the risk of acute coronary syndrome, myocardial infarction [1, 2], stroke [3], destabilization of blood pressure in patients with arterial hypertension [4], and the worsening of edematous syndrome in patients with heart failure have been described [4]. This information formed the basis of the developed and published recommendations, algorithms for rational choice, and use of NSAIDs in patients with various comorbidities [5]. These recommendations and procedures are intended for physicians who must choose the optimal strategy for using NSAIDs considering all risks. However, in real-life clinical practice, patients often start taking NSAIDs on their own and without considering all recommendations and algorithms. This applies not only to patients with cardiovascular diseases but also to those with other comorbidities, including chronic kidney disease. In this case, patients can take several drugs simultaneously and use different administration routes for a period ranging from several months to several years. This situation is aggravated by the fact that physicians are often unaware of patients taking NSAIDs on their own, or, unfortunately, do not always keep this possibility in mind. The problem of patients with cardiovascular comorbidity taking NSAIDs remains unresolved in real-life clinical practice.

The **objective** of this study was to assess the frequency and peculiarities of the usage of NSAIDs in patients with cardiovascular diseases admitted to the Emergency Cardiology Department.

Materials and methods

This study enrolled 190 patients (87 women and 103 men, mean age 62.05 ± 11.11 years) admitted to the Emergency Cardiology Department of the Saratov Regional Clinical Hospital from January to March 2020. This study was scheduled to continue until December 2020 in order to obtain a large sample of patients with subsequent analysis of the peculiarities of the usage of NSAIDs in real-life clinical practice for various cardiovascular diseases. Unfortunately, due to the COVID-19 pandemic, the recruitment of patients was suspended. However, it was decided to publish some preliminary data. This was a full-design study. The questionnaire

survey was conducted for all patients hospitalized during this period, except for patients with dementia (23 points or less on the Montreal Cognitive Assessment Scale [6]). All patients signed informed consent to participate in the study. The questionnaire included questions on the use of NSAIDs, reasons for their use, and peculiarities of their use during the month before hospitalization. The use of acetylsalicylic acid in low doses as antiplatelet therapy was not considered NSAID use.

Statistical processing of the obtained data was carried out using Statistica 8.0 software (StatSoft Inc. USA). Normally distributed quantitative characteristics are presented as M ± SD, where M is arithmetic mean, SD is standard deviation. The median (Me) and interquartile range [25th; 75th percentile] were used to describe parameters with distribution other than normal. Comparison of two groups was carried out using Student's t-test or Mann-Whitney test (if distribution was other than normal). A 2 × 2 table (Fisher's exact two-sided test, χ^2-test with Yates correction) was used to compare relative frequencies in two groups. Differences were considered significant at $p < 0.05$.

The structure of cardiac pathology in patients enrolled in this study is presented in Table 1. Acute coronary syndrome and decompensation of heart failure were the reasons for hospitalization in most patients. Ischemic heart disease (IHD) in 116 (71%) patients was represented by its acute forms, unstable angina and myocardial infarction. These were the onset of ischemic heart disease in 51 patients (44%); 65 patients (56%) had a history of IHD in different forms. The diagnosis of acute coronary syndrome was established based on European recommendations for the management of patients with this disease [7, 8]. At the time of present hospitalization, 48 (29%) patients were diagnosed with chronic forms of IHD without symptoms of acute coronary syndrome. Exertional angina as the only form of IHD was found in 12 patients (7%); a history of myocardial infarction was revealed in 36 patients (21%), including 25 patients currently suffering from exertional angina. Among 162 patients with signs of chronic heart failure (CHF), 56 patients (35%) were diagnosed with acute decompensation of heart failure [9]. In 34 patients, acute decompensation of CHF was the main reason for hospitalization. Patients without acute decompensation at the time of hospitalization mostly had CHF functional classes II and III (47% and 33%, respectively). Most patients with acute decompensation of CHF (70%) were diagnosed with CHF functional class III in the period before decompensation.

Such routine cardiovascular risk factors as smoking and overweight were analyzed in patients enrolled in this study. Smoking at the time of hospitalization was registered in 52 patients (27%). A history of smoking was reported by 43 patients (23%); 28 of them (15% of the total number enrolled in the study) quit smoking less than a year ago. Therefore, 80 patients (42%) currently smoke or stopped smoking less than a year ago; 69 of them (86%) were male. Therefore, 69 (67%) male patients admitted to the Emergency Cardiology Department had such a cardiovascular risk factor as smoking. Smoking was also registered in 11 female patients (13%), which is significantly less than in male patients ($p = 0.0001$). The smoking index was also higher in men than in women: 20 [10; 25] and 13 [7; 15], respectively, $p = 0.014$. Overweight (body mass index more than 25 kg/m^2) was observed in 101 (53%) patients — 60 men and 41 women. The distribution of the analyzed risk factors according to gender is presented in Fig. 1.

Table 1. *The cardiovascular diseases in patients*

Index	Value
The reason for hospitalization, abs (%):	
• acute coronary pathology	116 (61%)
• decompensated heart failure	34 (18%)
• rhythm disturbances	21 (11%)
• hypertensive crisis against the background of uncontrolled arterial hypertension	15 (8%)
• pulmonary embolism	4 (2%)
Clinical forms of cardiac pathology, abs (%):	
• arterial hypertension	168 (88%)
• coronary heart disease	164 (86%)
• chronic heart failure	162 (85%)
• atrial fibrillation	60 (32%)
Functional class of chronic heart failure in patients without acute decompensation, abs (%):	
• I	11 (10%)
• II	50 (47%)
• III	34 (33%)
• IV	11 (10%)
Functional class of chronic heart failure preceding acute decompensation, abs (%):	
• I	0 (0%)
• II	9 (16%)
• III	39 (70%)
• IV	8 (14%)

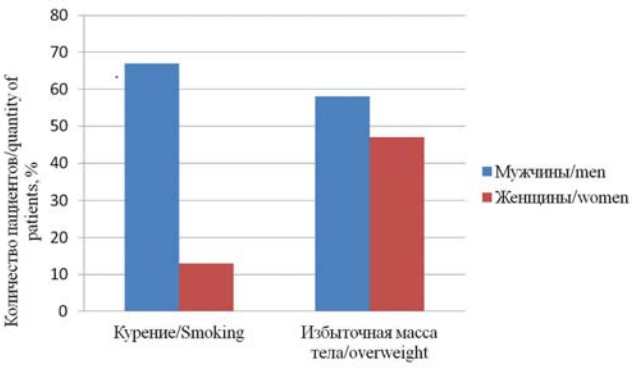

Figure 1. *Distribution cardiovascular risk factors in patients according to gender*

Comorbidity was analyzed in this study only based on the questionnaire filled by the patients on their own. Patient awareness of nosological forms requiring administration of NSAIDs was of particular interest. The following are the comorbidities indicated in the questionnaire by the patients on their own: disease of the gastrointestinal tract — 46 (24%) patients, diabetes mellitus — 36 (19%) patients, osteoarthritis — 24 (13%) patients, cancer — 7 (4%), gout — 6 (3%) patients.

This study did not analyze other medications used, including cardiotropic agents, since its purpose was to investigate the peculiarities and frequency of NSAID usage.

Results

One month before hospitalization, 92 (48%) patients took NSAIDs for different reasons: 42 (46%) men and 50 (54%) women. The mean age of these patients was higher than that of patients who did not require NSAIDs (63.98 ± 11.62 years and 60.20 ± 10.27 years, respectively, p = 0.018). Among the surveyed patients, 30 (16%) occasionally took NSAIDs but did not need to take them during the last month. Therefore, occasional use of NSAIDs over a longer period was observed in 122 (64%) patients: 57 men (47%) and 65 women (53%).

The main reasons, frequency, and duration of NSAID use one month before hospitalization are presented in Table 2. «Joint pain» as the main or one of the reasons for taking NSAIDs was indicated by 43 (47%) patients, headache — by 40 (43%) patients, back pain — by 30 (33%) patients. Almost half of the patients taking NSAIDs in the last month had been taking them for more than three years. During the month before hospitalization, 57 patients (62%) took NSAIDs at least once a week. That is one-third of the total number of patients enrolled in this study.

The following non-selective NSAIDs agents were the most commonly used: diclofenac — 37 (40%) patients, ibuprofen — 35 (38%) patients, ketorolac — 23 (25%) patients. Patients took the following selective NSAIDs less frequently: nimesulide — 22 (24%) patients, meloxicam — 13 (14%) patients; and coxibs were used only by 7 (8%) patients. An important aspect of self-treatment by patients is the fact that 26 (28%) patients simultaneously took two or more NSAIDs during the previous month. Most patients (59; 64%) took NSAIDs per os; intramuscular injections were used by 15 (16%) patients; the combination of simultaneous oral and intramuscular administration was used by 11 (12%) patients; other combinations, including intravenous and rectal administration — by 7 (8%) patients.

Table 2. *The reasons for taking NSAIDs, distribution of patients depending on the duration and frequency of taking NSAIDs during the last month*

Index	Value
The reasons for taking NSAIDs, abs. (%):	
• joint pain	43 (47%)
• headache	40 (43%)
• back pain	30 (33%)
• toothache	15 (16%)
• chest pain	14 (15%)
• musculoskeletal pain	11 (12%)
The duration of taking NSAIDs, abs. (%):	
• less than 3 months	14 (15%)
• from 3 months to 1 year	6 (7%)
• from 1 year to 3 years	27 (29%)
• more than 3 years	45 (49%)
Frequency of taking NSAIDs in the last month before hospitalization, abs. (%):	
• daily	13 (14%)
• 3 times a week	13 (14%)
• 2 times a week	13 (14%)
• once a week	18 (20%)
• less than once a week, but more often than once every 3 months	19 (21%)
• once within 3 — 6 months	16 (17%)

Only 55 (60%) patients used NSAIDs as prescribed by their physicians. Physicians inquired about cardiovascular diseases in 34 cases (62%). 37 patients (40%) used NSAIDs on their own, without recommendation by a physician.

Most patients (57; 62%) could not tell the potential adverse effects of NSAIDs. The possibility of kidney damage when taking NSAIDs was mentioned by 22 (24%) patients, liver damage — by 23 (25%) patients, cardiovascular disorders — by 6 (7%) patients, and gastric and intestinal lesions — by 10 (11%) patients. The possibility of damage to all these organs was mentioned by 11 (12%) patients. 45 (49%) patients took gastroprotectors. 6 (6.5%) patients reported worsening of edematous syndrome and increased blood pressure in connection with NSAIDs.

Laboratory tests revealed that hemoglobin level was significantly lower in patients who took NSAIDs one month before hospitalization than in patients who did not take NSAIDs (134 [122; 148] g/l and 144 [131; 151] g/l, respectively, p = 0.004). Anemia (decrease in hemoglobin level below 120 g/l in women and below 130 g/l in men) was found in 20 (22%) patients who took NSAIDs one month before hospitalization. No statistical differences were found in the incidence of anemia in patients taking NSAIDs (20; 22%) and in patients not taking these agents (14; 14%) (p = 0.177). This may be due to an insufficient number of patients in the compared groups. Therefore, analysis of the incidence of anemia due to NSAIDs requires further investigation when the study resumes.

Discussion

Almost half (48%) of patients admitted to the Emergency Cardiology Department took NSAIDs one month before hospitalization. Most of the patients belonged to the elderly population and had cardiovascular comorbidity. The reasons why patients with significant cardiovascular disease had to use NSAIDs do not differ from those in the general population of the corresponding age. Most patients cited joint pain, back pain and headaches as the reason for taking NSAIDs. Many patients (43%) listed several reasons for using NSAIDs. Our data match the results of the European study of NSAIDs in real-life clinical practice, suggesting that joint pain syndrome is one of the main reasons forcing patients to take NSAIDs for a long time and in high doses [1, 2].

We currently have results of a meta-analysis indicating that the risk of myocardial infarction associated with NSAIDs increases within one to seven days and when taking various drugs, including naproxen, which was considered relatively safe [2]. Of note is a small proportion of patients taking highly selective COX-2 inhibitors (coxibs) — agents with the lowest risk of gastrointestinal (GI) adverse events. However, a large proportion of patients had a high risk of gastrointestinal damage while taking NSAIDs. This is due to the use of antiplatelet agents and/or anticoagulants, the patients' age, possible ischemic lesions of the gastrointestinal mucosa with underlying severe cardiac disease. The rare prescription of coxibs in this category of patients is probably associated with the fear of cardiovascular emergencies. However, recent studies showed that these complications are class-specific; they can develop with any NSAIDs, and the probability of their occurrence is determined by individual features and the dose of a particular agent [1–4].

Taking NSAIDs per os is currently considered the most rational route of administration. It is on par with other methods in terms of effectiveness but has a better safety profile. The advantage of the parenteral route of administration is only in the rapid effect. However, the effect lasts only in the first days of treatment [5]. In real-life clinical practice, more than a third of examined patients used different routes of administration, including unjustifiably frequent and long parenteral use, or simultaneous use of different routes of administration and different NSAIDs, which significantly increases the risk of adverse events.

This study revealed that 62% of patients taking NSAIDs had to take these agents at least once a week. In total, a third of urgently admitted patients took NSAIDs regularly and frequently. In addition, most patients took the drugs for more than three years.

It should also be noted that 40% of patients took NSAIDs on their own, without the recommendation of their physician. This is crucial, given the low awareness of the possible side effects of NSAIDs among patients. The lack of patient awareness of the nosology for taking such agents was also revealed. Most of the examined patients who took NSAIDs also required proton pump inhibitors. This is because additional gastroprotective therapy is recommended during the combined use of antiplatelet agents and/or anticoagulants with NSAIDs [5]. However, only half of the patients who required proton pump inhibitors took them before hospitalization.

In our view, the lower hemoglobin level established in patients taking NSAIDs compared with those who did not take these agents one month before hospitalization is an important fact. There was no significant difference in the incidence of anemia among patients in the two groups, possibly due to the small number of patients.

Our study has several limitations. Firstly, we had to analyze information obtained from a relatively small group of patients since the study was suspended due to the COVID-19 pandemic. Secondly, the development of adverse events associated with NSAIDs was due to various reasons. However, we did not perform multivariate analysis in this paper. It will be performed in subsequent papers. The reason for taking NSAIDs — inflammatory disease, severity of inflammation, nociceptive or neuropathic pain, etc. — is certainly an important aspect. Differentiated analysis and the possibility of finding a relationship between NSAIDs and the destabilization of cardiovascular diseases and the development of emergency conditions require a large sample. We hope to resume this study.

Conclusion

Almost half of the patients admitted to the Emergency Cardiology Department took NSAIDs during the previous month before hospitalization. Most patients had to take NSAIDs frequently and regularly. Considering the plurality of medications taken for managing the underlying cardiovascular disease, the age of patients and comorbidities, NSAID use in this group of patients should not be uncontrolled. The possible use of NSAIDs in patients with cardiovascular comorbidity needs clarification since patients are poorly informed of the possible risks of adverse events when taking NSAIDs; they underestimate the danger and think it is unnecessary to inform physicians about the use of these drugs. Patients often take medications on their own, using different agents and different routes of administration simultaneously, thus increasing the risk of adverse events.

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