ORIGINAL INVESTIGATIONS

Pharmacogenetic aspects of the efficacy of nonsteroidal anti-inflammatory drugs and opioid analgesics for postoperative pain relief after total joint arthroplasty

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Objective: *to investigate possible associations between genetic, clinical, laboratory, and demographic parameters and the level of pain in the early postoperative (p/o) period, the need for opioid analgesics, and gastrointestinal symptoms in patients who underwent primary total knee (TKR) or hip replacement (THR).*

Material and methods. *Sixty-one patients hospitalized for THR or TKR were included in the study. P/o pain relief was achieved using nonsteroidal anti-inflammatory drugs (NSAIDs) – ketoprofen or ketorolac – with tramadol prescribed "on demand." Pain was assessed in all patients using the numeric rating scale (NRS) on postoperative days 1–5. The amount of opioid analgesics used during hospitalization was recorded. Gene polymorphisms of CYP2C9, CYP2C8, PTGS1, PTGS2, ABCB1, CYP2D6, OPRM1, COMT, and C3orf20 were analyzed using real-time polymerase chain reaction.*

Results and discussion. *Patients with the AC genotype of CYP2C9*3 experienced less intense pain on postoperative day 1 (4.5±1.0 vs. 7.0±2.3; p=0.03) and required fewer opioids during hospitalization (20.0±11.5 vs. 28.0±7.4 morphine equivalent units; p=0.04) compared to those with the AA genotype. Carriers of the CC genotype of the rs1045642 polymorphism of the ABCB1 gene reported less pain on day 5 (1.5±0.7 vs. 3.7±1.2; p=0.04) than those with the CT genotype. Patients with the AA genotype of rs1799971 in the OPRM1 gene required more opioids in p/o period than those with AG + GG genotypes (28.4±7.1 vs. 21.6±9.8 morphine equivalent units; p=0.03). Patients with the GG genotype of rs12496846 in the C3orf20 gene experienced more intense pain on p/o day 4 (6.0±1.41) than those with the AA genotype (2.60±1.50; p=0.002).*

Conclusion. *Following THR and TKR, pain intensity and/or opioid use were associated with patients' pharmacogenetic profiles in CYP2C9, ABCB1, OPRM1, and C3orf20.*

Keywords: *total joint arthroplasty; postoperative pain; pain management; pharmacogenetics; nonsteroidal anti-inflammatory drugs; opioid analgesics.*

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The development and introduction into routine practice of total endoprosthesis replacement of joints is one of the most important achievements of modern orthopedic surgery [1]. As with any reconstructive surgery, replacement of the hip and knee joints is accompanied by pronounced postoperative pain [1]. Inadequate analgesia in the early and late postoperative period is associated with untimely activation, delayed rehabilitation process, which increases the length of hospitalization, increases risk of infectious and thrombotic complications, and also contributes to chronic pain [1]. According to the recommendations regarding the main components of multimodal analgesia for accelerated recovery in the postoperative period (Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery, ERAS), the first line of analgesia is a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol; in case of their ineffectiveness, opioids are added using pro re nata (PRN) regimen [2].

The group of NSAIDs includes numerous drugs with heterogeneous chemical structure, but with a common mechanism of pharmacological action based on the inhibition of prostaglandin biosynthesis from arachidonic acid under the action of the enzyme cyclooxygenase [3, 4]. The biotransformation of NSAIDs in the liver occurs with the involvement of cytochrome system isoenzymes P450, the most significant of which is CYP2C9 [5]. According to the data of Clinical Pharmacogenetics Implementation Consortium, certain genotypes suggest patients' CYP2C9 phenotypes: «normal» metabolizers correspond to *CYP2C9*1/*1*, «intermediate» metabolizers – *CYP2C9*1/*2*, *CYP2C9*1/*3*, *CYP2C9*2/*2* or other rarer, and «slow» metabolizers – for example, persons with *CYP2C9*2/*3* or *CYP2C9*3/*3* [4]. Fur-

thermore, the "intermediate" metabolizers are divided into two subgroups according to the activity index (AI): AI 1.5 is noted in carriers of *CYP2C9*1/*2* AI 1 – in carriers of *CYP2C9*1/*3*, *CYP2C9*2/*2* [4]. "Intermediate" metabolizers with AI 1.5 and "normal" metabolizers for CYP2C9 are characterized by similar response rates to NSAIDs, and the use of standard doses of NSAIDs is recommended for patients in these groups by the Clinical Pharmacogenetics Implementation Consortium. Patients belonging to the group of "intermediate" metabolizers with AI 1 are characterized by a slower rate of biotransformation of NSAIDs and a higher risk of adverse reactions, therefore, recommendations have been developed for them, as for "slow" metabolizers of CYP2C9 to personalize therapy with certain NSAIDs using reduced doses or alternatively metabolizable drugs of this group [4].

Currently, there are studies of the effect of polymorphisms of the *CYP2C9* gene on the pharmacokinetics of individual NSAIDs and on the development of adverse reactions from the gastrointestinal tract (GIT), however, there are few studies on the relationship between the patient's *CYP2C9* genotype and the analgesic effect of NSAIDs [5–12]. It is also necessary to investigate the influence of non-genetic factors (age, gender, concomitant diseases, surgical features, medications taken together) on the effectiveness of analgesic therapy in patients after knee or hip arthroplasty.

The aim of the study was to investigate possible associations of genetic, clinical, laboratory, and demographic parameters with the level of pain in the early postoperative period, the need for opioid analgesics, and gastrointestinal symptoms in patients who underwent primary knee or hip replacement.

Material and methods

Patients and clinical outcomes. The study was approved by the Ethics Committee of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of the Russian Federation (Protocol №14 dated 09/29/2022). All participants signed a voluntary informed consent to participate in the study, to give store and use their biological material.

The open prospective observational study was conducted for 9 months (from February to October 2023) and included a preoperative visit and an inpatient phase. The study involved 61 patients undergoing inpatient treatment at the traumatology Department №1 of the Moscow State Medical University "O.M. Filatov Municipal Clinical Hospital No.15 of the Moscow Department of Health".

The criteria for inclusion in the study were: age over 18 years in male and female patients, prolonged pain, outpatient NSAID intake >1 month, the presence of coxarthrosis and/or gonarthrosis, for which patients were hospitalized for elective hip or knee joint replacement.

Non-inclusion criterion: the presence of contraindications to the use of NSAIDs (regulated in the instructions for medical use approved by the Ministry of Health of the Russian Federation).

The researchers conducted a detailed collection of pharmacological history, as well as data on concomitant pathology and therapy. To assess the intensity of pain in the postoperative period (from day 1 to day 5), a numerical rating scale (NRS) was used, where 0 corresponded to no pain, and 10 – to unbearable pain. All patients underwent standard postoperative anesthesia with ketoprofen at a dose of 100 mg or ketorolac at a dose of 30 mg 1–2 times a day. The opioid analgesic tramadol was prescribed at a dose of 100 mg if there was a need for additional pain relief. The amount of tramadol used for pain complaints during the entire time of hospitalization was summed up and converted into the equivalent of morphine for intravenous administration: 100 mg of tramadol was equivalent to 10 mg of morphine, which is accepted as universal units for accounting for opioid analgesics consumed [13]. The study was conducted without the intervention of a researcher in prescribing pain therapy.

Selection of candidate genes and molecular genetic research. Based on the data from the specialized PharmGKB resource (The Pharmacogenetics and Pharmacogenomics Knowledge Base, https://www.pharmgkb.org /) and taking into account the recommendations of the Clinical Pharmacogenetics Implementation Consortium, the following markers were selected for molecular genetic research: gene polymorphisms, the products of which may be associated with the pharmacokinetics and pharmacodynamics of NSAIDs, *CYP2C9* (rs179985, rs1057910) [4], *CYP2C8* (rs10509681, rs11572080) [8], *PTGS1* (rs10306135, rs12353214) [14] and *PTGS2* (rs20417) [15], with ketoprofen transport – *ABCB1* (rs1045642; presumably, it can be a substrate of P-glycoprotein by analogy with dexketoprofen [16]), with the pharmacokinetics and pharmacodynamics of the opioid analgesic tramadol – *CYP2D6* (rs3892097, rs1065852, rs28371725, rs5030656) [17, 18], *OPRM1* (rs1799971) [19], *COMT* (rs4680) [20], as well as polymorphism of the gene that predicts the need for analgesia according to a genome–wide association study – *C3orf20* (rs12496846) [21].

Venous blood from the ulnar vein was collected into a vacuum tube containing EDTA-K2. Blood and DNA samples were stored at -80 °C until the moment of the study. The laboratory work was performed at the Research Institute of Molecular and Personalized Medicine of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of the Russian Federation. Genomic DNA was isolated from whole blood using a silicon sorbent (Syntol, Russia). Genotyping was performed by real-time polymerase chain reaction on a CFX96 Touch Real-Time System device with CFX Manager software version 3 (Bio-Rad, USA) using commercial reagent kits (Syntol; TestGen, Russia).

Statistical processing of the results was performed using the standard StatSoft Statistica 10.0 application software package. Qualitative indicators are reflected in the form of absolute values and percentages. The frequency distribution of the genotypes of the studied pharmacogenetic markers was checked for compliance with the Hardy–Weinberg equation. To identify differences in the frequency distribution of the studied polymorphisms between the groups and to assess their statistical significance, the 2 criterion was used; with a small number of observations, the exact Fisher criterion was calculated. To assess the relationship between the studied indicators, the odds ratio of the event was calculated with a 95% confidence interval. The differences were considered significant at $p<0.05$.

Results

Clinical data. The study included 61 patients: 24 men (39.34%) and 37 women (60.65%), the median age was 64.0 [59.0; 70.0] years. The patients had the following concomitant diseases: arterial hypertension, coronary artery disease (n=50, 81.9%), history of peptic ulcer of the stomach or duodenum (n=6, 9.8%), type 2 diabetes mellitus (n=5, 8.1%), bronchial asthma / chronic obstructive pulmonary disease (n=4, 6.5%), chronic kidney disease (n=2, 3.2%), rheumatoid polyarthritis (n=1, 1.6%). At the outpatient and inpatient stages, patients took the following drugs: omeprazole

(n=52, 85.2%), angiotensin converting enzyme inhibitors and beta-blockers (n=42, 68.8%), statins (n=15, 24.5%), clopidogrel/ticagrelor (n=13, 21.3%), acetylsalicylic acid (n=12, 19.6%), antidiabetic drugs (biguanides, Na+-glucose co-transporter type 2 inhibitors (n=5, 8.1%), glucocorticoids (n=4, 6.5%), methotrexate (n=1, 1.6%). At the inpatient and outpatient stage, 51 out of 61 patients took NSAIDs, only at the outpatient stage – 10 patients. At the inpatient stage, 51 patients were anesthetized with NSAIDs in the form of intramuscular and/or intravenous injections: ketorolac – 28 and ketoprofen – 23. The average duration of the therapy was 5.05±2.15 days. In 10 patients, NSAIDs were not used after the surgery, they received only tramadol.

In all patients (n=61), the indication for prescribing NSAIDs at the prehospital stage was chronic pain associated with osteoarthritis of the hip or knee joint. The characteristics of the patients are presented in Table 1.

The results of genotyping. The genotype distribution data is shown in Table 2. The distribution of alleles and genotypes for all studied polymorphisms corresponded to the Hardy–Weinberg equilibrium (p>0.05), with the exception of rs4680 *COMT* (χ^2= 9.5, p=0.001). The interpretation of diplotypes and phenotypes for *CYP2C9* was carried out in accordance with the recommendations of the Clinical Pharmacogenetics Implementation Consortium (Table. 3) [4].

The patients were divided into three groups according to the predicted phenotype based on the diplotype and AI for *CYP2C9* (Table 4).

Table 1. Patient characteristics

Indicator	Value
Age, years	63.83±10.31
Female, n	37
Hemoglobin, g/L	134.50±17.93
Platelets, $\cdot 10^9$/L	259.72±65.31
Red blood cells, $\cdot 10^{12}$/L	4.44±0.47
Leukocytes, $\cdot 10^9$/L	7.50±2.25
Creatinine, μmol/L	100.93±22.95
GFR CKD-EPI, ml/min/1.73 m^2	60.39±15.94
AST, IU/L	29.13±14,81
ALT, IU/L	26,73±18.50
Total protein, g/l	70.71±6.59
NRS pain:	
Day 1	6.83±2.35
Day 2	4.65±2.10
Day 3	3.94±2.13
Day 4	3.64±2.48
Day 5	2.73±1.22
The average pain level for 5 days	4.91±1.73
Morphine equivalent in 5 days, units	27.50±7.94

Note. The data is presented as M±SD, unless otherwise specified. GFR – glomerular filtration rate; AST – aspartate aminotransferase; ALT – alanine aminotransferase.

Taking into account the diplotype, AI, and the suspected phenotype for *CYP2D6* [18], groups of "normal" (n=39, 63.9%) and "intermediate" (n=22, 36.1%) metabolizers for *CYP2D6* were identified.

Associative analysis – pain level, amount of opioid analgesics used. Patients with the AC genotype of *CYP2C9*3* had significantly less pronounced pain on the 1st day of the postoperative period, as well as a lower need for opioids during the entire hospitalization than those with the AA genotype (Table 5). At the same time, patients with the AA genotype of *CYP2C9*3* were significantly older than patients with the AC genotype (mean age was 64.87 and 49.00 years, respectively; p=0.002). There were no other statistically significant differences in clinical and laboratory parameters between these groups.

Regarding *CYP2C9*2*, there were no statistically significant differences in pain intensity in patients with the CC genotype and carriers of the CT + TT genotype on the 1st (6.86 and 6.80. respectively; p=0.93), 2nd (4.77 and 4.30; p=0.53), 3rd (4.16 and 3.22; p=0.25), 4th (4.00 and 1.75; p=0.09) and 5th (10.61 and 3.00; p=0.79) days of the postoperative period, as well as in morphine equivalent (27.29 and 29.09 units; p=0.50).

The comparison of patients by *CYP2C9* phenotype groups revealed significant differences in pain levels and the need for opioid analgesics, expressed in morphine equivalent. Thus, on the 1st day after surgery, "intermediate" metabolizers with AI 1 experienced the least pain compared with the group of "normal" metabolizers (on average, 4.8±1.1 and 7.1±2.3 on NRS, respectively; p=0.03) and needed less additional prescription of opioid analgesics during hospitalization compared with "intermediate" metabolizers with AI 1.5 (on average 20.4±9.9 and 29.1±5.8 units in morphine equivalent (p=0.01).

Patients belonging to these phenotypic groups were comparable in all clinical, demographic and laboratory parameters, with the exception of age – the "normal" metabolizers for *CYP2C9* were older than the "intermediate" metabolizers with AI 1 (average age – 65.7±9.8 and 52.8±11.47 years, respectively; p=0.008), – as well as the platelet count in the total blood count upon admission (249.2±66.7 and 319.0±55.1·10^9/L, respectively; p=0.02).

Patients with the CC genotype of rs1045642 *ABCB1* had less pronounced pain on the 5th day of the postoperative period compared with carriers of the CT genotype (1.5±0.7 and 3.7±1.2 on NRS, respectively; p=0.04). It should be noted that patients with CC and CT genotypes were comparable in all clinical, demographic, and laboratory characteristics.

With respect to rs1799971 *OPRM*, it was shown that patients with genotypes AA and AG + GG had similar pain levels in the postoperative period, but differed in the amount of morphine equivalent: patients with genotype AA required more opioids in the postoperative period than patients with genotype AG + GG (28.4±7.1 and 21.6±9.8 units, respectively; p=0.03). Groups of patients with AA and AG + GG genotypes of rs1799971 were comparable in clinical, demographic and laboratory parameters.

When studying the polymorphism of *C3orf20* rs12496846, significant differences were found between the groups: patients with the GG genotype had more severe pain on the 4th day of the postoperative period (6.0±1.41) than carriers of AA genotype (2.60±1.50); p=0.002.

No significant associations of rs11572080 and rs10509681 carriage of the CYP2C8 gene, rs10306135 and rs12353214 of the PTGS1 gene, rs20417 of the PTGS2 gene, rs3892097, rs1065852, rs28371725, rs5030656 of the CYP2D6 gene, rs4680 of the COMT

Table 2. Genotype distribution of studied polymorphic variants

Gene	Polymorphism	Genotype	Number of patients, n (%)	Allele, %	
CYP2C9	*CYP2C9*2* rs1799853	CC CT TT	48 (78.7) 12 (19.7) 1 (1.6)	C (88.5)	T (11.5)
CYP2C9	*CYP2C9*3* rs1057910	AA AC	57 (93.4) 4 (6.6)	A (96.7)	C (3.3)
PTGS2	rs20417	CC CG GG	38 (62.3) 20 (32.8) 3 (4.9)	C (78.7)	G (21.3)
PTGS1	rs10306135	AA AT TT	39 (63.9) 18 (29.5) 4 (6.6)	A (78.7)	T (21.3)
PTGS1	rs12353214	CC CT TT	40 (65.6) 20 (32.8) 1 (1.6)	C (82.0)	T (18.0)
CYP2C8	rs10509681	TT TC CC	51 (83.6) 9 (14.8) 1 (1.6)	T (91.0)	C (9.0)
CYP2C8	rs11572080	CC CT	51 (83.6) 10 (16.4)	C (91.8)	T (8.2)
ABCB1	rs1045642	CC CT TT	16 (26.2) 30 (49.2) 15 (24.6)	C (50.8)	T (49.2)
OPRM1	rs1799971	AA AG GG	54 (88.52) 6 (9.84) 1 (1.64)	A (93.4)	G (6.6)
COMT	rs4680	GG GA AA	17 (27.9) 26 (42.6) 18 (29.5)	G (49.2)	A (50.8)
CYP2D6	*CYP2D6*4* rs3892097	GG GA	40 (65.6) 21 (34.4)	G (82.8)	A (17.2)
CYP2D6	*CYP2D6*6* rs5030655	AA A/delA	60 (98.4) 1 (1.6)	A (99.2)	delA (0.8)
CYP2D6	*CYP2D6*10* rs1065852	CC CT	39 (63.9) 22 (36.1)	C (82.0)	T (18.0)
CYP2D6	*CYP2D6*41* rs28371725	CC CT	53 (86.9) 8 (13.1)	C (93.4)	T (6.6)
CYP2D6	*CYP2D6*9* rs5030656	AAG/AAG AAG/delAAG	60 (98.4) 1 (1.6)	AAG (99.2)	delAAG (0.8)
C3orf20	rs12496846	AA AG GG	29 (47.5) 23 (37.7) 9 (14.8)	A (66.4)	G (33.6)

gene with the severity of pain in the early postoperative period, as well as with the need for opioids for morphine equivalent throughout hospitalization were found (p>0.05).

Discussion. According to current data, the need for hip joint replacement will increase by 174% by 2030, and knee joint replacement by 673% [22]. Achieving optimal pain control after arthroplasty of large joints is a priority for both surgeons and patients [23]. The Society for Enhanced Recovery After Surgery (ERAS) has developed and implemented recommendations for multimodal analgesia, including the first-line use of NSAIDs in combination with paracetamol [2]. Foreign authors analyzed 60 randomized controlled trials, more than half of which used NSAIDs, and there was a statistically significant decrease in morphine demand when NSAIDs were added to the therapy regimen, as well as a decrease in the incidence of adverse reactions (nausea and vomiting) associated with opioid use [24]. Thus, NSAIDs in pain management have an opioid-sparing effect, increase the effectiveness and safety of pain relief [25].

The present study was not large enough to form unambiguous conclusions; however, it allowed us to establish important patterns that require further clarification. It was shown that the genetic characteristics of patients are associated with the level of pain and the need for opioid analgesics, in particular, the presence of the polymorphism CYP2C9*3 (rs1057910) was associated with a lower severity of pain on the 1st day of the postoperative period, as well as with a lower morphine equivalent during the entire hospitalization. This is probably caused by a genetically determined decrease in the metabolic activity of the CYP2C9 enzyme, a slowdown in the biotransformation of NSAIDs and an increase in their plasma concentration [4]. In this case, ketorolac and ketoprofen were used in the postoperative period, as the role of the CYP2C9 enzyme in biotransformation of these drugs remains controversial (for ketoprofen) or is considered insignificant (for ketorolac) [4]. Similar results regarding ketoprofen, ketorolac and CYP2C9 were obtained earlier in the works with the participation of our team and require further confirmation [15, 26]. When analyzing the rs179985 polymorphism of CYP2C9 (CYP2C9*2), there were no statistically significant differences in pain intensity between carriers of different genotypes. This may be explained by the fact that this polymorphism causes a decrease in the enzyme function, while CYP2C9*3 causes complete absence of its function [4]. At the same time, our study showed that patients with CYP2C9 genotypes*1/*3 and CYP2C9*2/*2 , who belong to the "intermediate" metabolizers with AI 1 (have a marked decrease in the enzyme activity), were also characterized by less pronounced pain on the 1st day of the postoperative period and needed opioid analgesics less, which is mainly due to the contribution of the CYP2C9*3 polymorphism (4 out of 5 patients in this group had the CYP2C9 genotype*1/*3 and 1 – the CYP2C9 genotype.*2/*2). Patients with these diplotypes are recommended to be treated with alternative drugs from the NSAID group, whose metabolism is not associated with the CYP2C9 enzyme, or to take the minimum doses of NSAIDs indicated in the instructions, which have the shortest half-life [4].

Table 3. Interpretation of pharmacogenetic testing results for *CYP2C9*

*CYP2C9*2* genotype rs1799853	*CYP2C9*3* genotype rs1057910	Diplotype	The phenotype predicted by the diplotype
CC	AA	*CYP2C9*1/*1*	«Normal metabolizers»
CT	AA	*CYP2C9*1/*2*	«Intermediate» metabolizers with AI 1
TT	AA	*CYP2C9*2/*2*	«Intermediate» metabolizers with AI 1.5
CC	AC	*CYP2C9*1/*3*	«Intermediate» metabolizers with AI 1
CT	AC	*CYP2C9*2/*3*	«Slow» metabolizers
CC	CC	*CYP2C9*3/*3*	«Slow» metabolizers

Table 4. Distribution of patients by diplotype and phenotype for *CYP2C9*

Diplotype	AI	Number of patients, n (%)	The *CYP2C9* phenotype predicted by the diplotype
*CYP2C9*1/*1*	2	44 (72.1)	«Normal metabolizers»
*CYP2C9*1/*2*	1.5	12 (19.7)	«Intermediate» metabolizers with AI 1.5
*CYP2C9*1/*3. CYP2C9*2/*21*	1	5 (8.2)	«Intermediate» metabolizers with AI

Table 5. Postoperative pain intensity according to the NRS and opioid requirement by presence of *CYP2C9*3* (rs1057910), M±SD

NRS pain	*CYP2C9*3* genotype		p
	AA	AC	
Day 1	**7.0±2.3**	**4.5±1.0**	**0.03**
Day 2	4.7±2.1	3.3±0.5	0.26
Day3	3.9±2.1	3.6±1.5	0.81
Day 4	3.5±2.5	4.5±2.1	0.61
Day 5	2.8±1.7	3.1±1.09	0.79
Morphine equivalent in 5 days, units	**28.0±7.4**	**20.0±11.5**	**0.04**

It is known that CYP2D6 is the main enzyme for converting tramadol into an active metabolite with analgesic effect [17, 23]. Our study found no significant associations between pain intensity and the presence of CYP2D6 gene polymorphisms, which may be due to the fact that tramadol was prescribed "on demand" in most patients with severe pain on the background of NSAID analgesic therapy and its possible ineffectiveness in carriers of slow CYP2D6 allelic variants was elusive. In addition, there were no "slow" CYP2D6 metabolizers in the study sample, who were advised to avoid tramadol due to the high risk of its ineffectiveness.

In 10 patients who underwent hip or knee joint replacement, analgesic therapy was performed with tramadol alone (without NSAIDs), which can be considered an inadequate tactic in the absence of contraindications to NSAIDs. The practice of avoiding paracetamol in addition to NSAIDs (multimodal analgesia) should also be recognized as inadequate anesthesia [27–29]. Another limitation of this study is the inappropriate duration of administration of parenteral forms of ketoprofen and ketorolac in some patients (on average 5.05±2.15 days), which contradicts the instructions for the medical use of these drugs. The study was conducted without interference with the prescribed therapy, however, the correct tactic in this case can be considered the transition to oral forms of drugs on the 2nd–3rd day after surgery, with continued adherence to the duration of ketorolac administration (no more than 5 days).

The lower value of the morphine equivalent in our study is explained by the carriage of the rs1799971 *OPRM1* polymorphism. This is inconsistent with the data that this polymorphism is associated with lower opioid analgesia efficiency and a large amount of opioid analgesics used, in particular morphine. However, information about this marker is generally contradictory, including regarding tramadol [17, 25, 30]. In our work, the data was obtained on a small (n=7) group of carriers of the rs1799971 *OPRM1* polymorphism and require further clarification.

In addition, carriers of the CT genotype of the rs1045642 gene *ABCB1* had significantly more pronounced pain on the 5th day of the postoperative period compared with patients with the CC genotype. It is known that the *ABCB1* gene encodes a P-glycoprotein, a membrane transporter present in various body tissues and responsible for the active transport of xenobiotics, which are its substrates, from the intracellular to the extracellular space for further excretion, and ketoprofen, as well as opioid analgesics morphine, fentanyl, and methadone are considered its probable substrates [16, 20]. The presence of polymorphism rs1045642 of the *ABCB1* gene is associated with a decrease in the expression of P-glycoprotein on the cell surface and the accumulation of its substrates.

Thus, our results are preliminary and contradict the hypothesis described above about the supposed greater efficacy of ketoprofen in carriers of this polymorphism and require further clarification of the role of glycoprotein P in response to therapy with ketoprofen and NSAIDs and opioid analgesics.

The present study analyzed patients with the rs12496846 polymorphism of the *C3orf20* gene, and it was shown that carriage of the GG genotype is accompanied by more pronounced pain. This was confirmed in a study by D. Nishizawa et al. [31], in which carriers of the G allele were characterized by decreased sensitivity to opioid analgesics and required increased analgesia.

Conclusion. Thus, the results of this study indicate that the level of postoperative pain and the amount of opioid analgesics consumed after knee or hip replacement were associated with the pharmacokinetic characteristics of patients with rs1057910 of the *CYP2C9* gene, rs1045642 of the *ABCB1* gene, rs1799971 of the *OPRM1* gene and rs12496846 of the *C3orf20* gene.

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