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Preemptive Analgesia with Nonsteroidal Anti-Inflammatory Drugs in the Perioperative Period

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Summary

Objective. A comparative assessment of the efficacy and safety of the preemptive use of ibuprofen and ketoprofen in patients undergoing elective surgery under general anesthesia.

Material and methods. A multicenter randomized prospective study included 58 patients grouped into 2 arms. Ibuprofen 800 mg in Group 1 (*N*=32), and ketoprofen 100 mg in Group 2 (*N*=26) were administered intravenously 30 minutes prior to surgical procedure, and afterwards every 12 hours during patient's stay in the intensive care unit. Efficacy and safety were assessed using a visual analog scale (VAS), patient's need in opioid analgesics, laboratory parameters (serum levels of cortisol, cystatin C, CBC, coagulogram, TEG) and instrumental methods (algesimetry — qNOX).

Results. VAS values were 32.4% lower in Group 1 vs Group 2 in the immediate postoperative period, *P*=0.003. By the end of Day 1 this difference was no longer visible following the use of promedol. There was a correlation between qNOX values at the end of surgery and VAS values at patient's waking up from anesthesia (*P*=0.0007). Cortisol plasma concentrations in groups 1 and 2 did not differ significantly, *P*=0.105. The average daily promedol consumption in Groups 1 and 2 was 42±17.5 mg/day and 50±19.7 mg/day, respectively, *P*=0.022. Cystatin C concentrations in the first morning after surgery was 0.95±0.29 mg/l in the ibuprofen group, and 1.19±0.43 mg/l — in the ketoprofen group, *P*=0.027. Signs of renal dysfunction were documented in 4 out of 32 patients (12, 5%) from Group 1, and in 10 of 26 (38.5%) patients from Group 2 since the end of surgery and up to the first postop morning, the Chi-squared value was 0.031. Hemostasis was not affected by NSAIDs use in both groups.

Conclusion. Ibuprofen provided more powerful analgesia, than ketoprofen in the postoperative period, while during surgical procedure both drugs showed similar anlgesic efficacy. Patients on ibuprofen required significantly fewer additional boluses of opioid analgesics. Both drugs showed no clinically significant effect on hemostasis and hematopoiesis. More rare occurrence of renal dysfunction in Group 1 patients is indicative of lower nephrotoxicity of ibuprofen.

Keywords: preemptive analgesia; anesthesia; nonsteroidal anti-inflammatory drugs; NSAIDs; ibuprofen; ketoprofen; perioperative period; automated monitoring of sedation; ICU

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

Introduction

Surgical intervention is a source of more or less persistent pain syndrome, and its control is one of the main tasks of the anesthesiologist. According to various data, more than 80% of patients suffer from post-operative pain, regardless of the type of surgery, and less than 50% consider the pain relief to be adequate [1–6]. This is a priority issue, as pain significantly affects patients' quality of life, activities of daily living, psychosocial functioning [6–11], and increases the need for medical care [12], including in the context of health insurance [13].

Importantly, despite similarities in the causes of pain, each patient experiences pain differently and therefore requires a personalized approach to pain management [14]. Pain assessment systems such as the CONOX method (using qNOX as a modifiable index of anesthesia) can be used to personalize pain management. However, the method is applicable intraoperatively under general anesthesia and it remains unclear how such personalization will affect analgesia in the postoperative period.

The concept of multimodal analgesia, including the use of non-steroidal anti-inflammatory drugs

(NSAIDs), opioids, local anesthetics and, in some cases, adjuvants such as gabapentin, is the cornerstone of quality analgesia [15]. The prophylactic administration of analgesics, mainly NSAIDs, in the preoperative period plays an important role in this approach [16–19]. However, intensive use of analgesics, including in the immediate postoperative period, is considered necessary for good-quality pain relief [20]. This approach has been shown to reduce postoperative pain intensity and the need for additional opioid analgesia [12, 21–26]. On the other hand, there are still questions about the safety of NSAIDs as part of pain management. It is well known that their use is limited by their safety profile due to possible renal damage, impaired blood coagulation, etc. [27–29]. Meanwhile, a Cochrane 2021 meta-analysis [21] suggests that the results of the perioperative use of NSAIDs are mixed and further research is needed. Finally, the paucity of publications on preemptive analgesia with intravenous ibuprofen is an important point.

We believe that our work will contribute to the development of preemptive analgesia strategies as a basis for multimodal analgesia in the perioperative period.

The aim of the study was to compare the efficacy and safety of the preemptive use of ibuprofen and ketoprofen in elective surgery under general anesthesia.

Materials and Methods

A multicenter randomized prospective study was conducted on the basis of the L. G. Sokolov North-Western District Scientific and Clinical Center and the I. I. Mechnikov North-West State Medical University in 2023, after approval by the local ethics committee (Protocol No. 4 of the meeting of the Local Ethics Committee of the L. G. Sokolov North-Western District Scientific and Clinical Center, dated March 27, 2023).

Patients were selected for inclusion in the study according to the criteria listed in Table 1. There was no preliminary calculation of the sample size and no blinding of the study participants; randomization was performed using the envelope method.

A total of 58 patients undergoing surgery for diseases of the thoracic (thoracoscopic) and urinary organs were studied; the mean age was 59.6±17.6 years (Tables 2, 3).

The patients were divided into 2 groups. In group 1 (*N*=32), patients received ibuprofen 800 mg as an intravenous drip 30 min before surgery and then every 12 h in the intensive care unit (ICU). Patients in group 2 (*N*=26) received ketoprofen 100 mg as an intravenous drip at the same time.

The study groups were comparable in terms of patient characteristics (Table 2). Three patients supposed to be included in group 2 were excluded due to the exclusion criteria (Table 1), resulting in different group sizes despite randomization.

The mean duration of surgery was 194.3±37.6 minutes. Average doses of drugs used for induction of anesthesia were 1.9±0.6 mg/kg propofol, 151.1±50.6 μg fentanyl; for maintenance of anesthesia were 1–3 vol% sevoflurane, 2–3 μg/kg/h fentanyl, 101.2±33.7 mg rocuronium bromide.

Table 1. Patient selection criteria for the study.

Inclusion criteria	1. Signed consent form 2. Males and females at least 18 years of age 3. Elective thoracic/urologic surgery
Non-inclusion criteria	1. Hypersensitivity to NSAIDs 2. Bronchial asthma 3. Erosive and ulcerative diseases of gastrointestinal tract 4. Liver failure 10–15 points on the Child-Pugh scale 5. Severe renal failure (creatinine clearance <50 mL/min) 6. Decompensated heart failure 7. Cerebrovascular or other hemorrhage (including intracranial hemorrhage) 8. Hemophilia and other blood coagulation disorders (including hypocoagulation) 9. Pregnancy or lactation 10. Children under 18 years of age
Postrandomization exclusion criteria	1. Withdrawal of informed consent 2. Refusal to follow up as per study protocol

Table 2. Patient characteristics.

Parameters	Values in groups		*P* value
	Ibuprofen	Ketoprofen	
Number	32	26	
Male, %	66.7	62.5	0.73
Age, years, median [min; max]	57 [38; 70]	61 [40; 73]	0.89
CHF (NYHA), median [min; max]	3 [1; 5]	3 [1; 5]	0.89
Rhythm disturbances, %	32.4	20.0	0.82
Type 2 diabetes mellitus, %	44.4	42.7	0.70
COPD, %	14.8	20.0	0.87
Body mass index >30, %	44.4	40.0	0.74

Note. CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease

Patients underwent the same type of anesthesia: induction of anesthesia was performed with propofol and fentanyl, sevoflurane and microjet injection of fentanyl were used to maintain anesthesia, depending on the stage of surgery. Relaxation was maintained with rocuronium bromide using TOF monitoring.

Harvard standard monitoring was used during surgery. In addition, the CONOX Fresenius Kabi (Germany) monitor, which evaluates the level of anesthesia and depth of hypnosis during general anesthesia, was used to assess the nociceptive response based on changes in the qNOX index. Simultaneous monitoring of qCON and qNOX indices allows clinical assessment of the level of anesthesia and measurement of the analgesic component as a predictor of response to various stimuli, which enables reduction of risks associated with anesthesia and optimization of hypnotic and analgesic doses. The latter value was recorded at the end of surgery. Otherwise, intensive postoperative therapy did not differ between the groups.

Table 3. Types of operations performed.

Type of surgery	Groups, *N* (%)	
	Ibuprofen	Ketoprofen
Upper lobectomy	7 (21.9)	8 (30.8)
Middle lobectomy	3 (9.4)	1 (3.8)
Lower lobectomy	6 (18.8)	2 (7.7)
Thymectomy	3 (9.4)	2 (7.7)
Bullae resection, pleurectomy	8 (25.0)	11 (42.3)
Kidney resection	5 (15.6)	2 (7.7)
Total	32 (100)	26 (100)

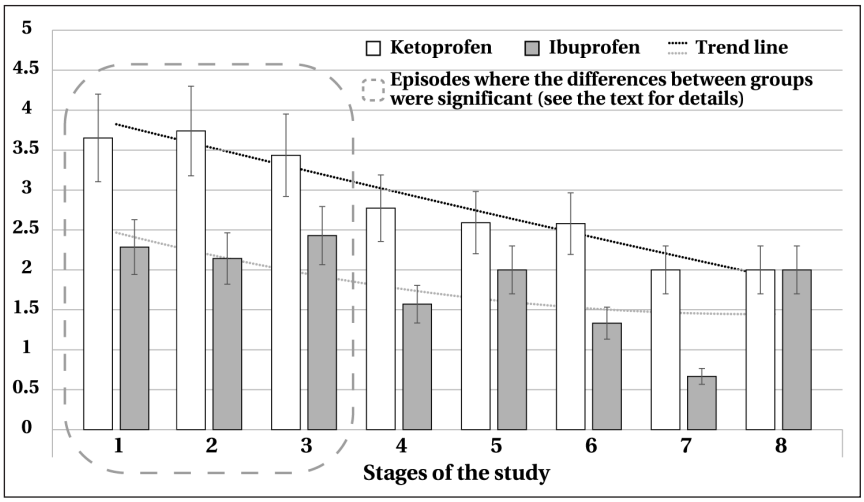

Fig. 1. Pain severity assessed using VAS in the post-op period.
Note. Horizontal axis shows 3-hour episodes of the postoperative period, vertical axis shows VAS score (cm) as mean value and standard deviation.

The postoperative period was divided into 8 stages. Efficacy and safety of analgesia were assessed by VAS every 3 hours from the moment of admission of the patient to the intensive care unit, as well as by the need for opioid analgesics and laboratory criteria (cortisol, cystatin C, CBC with reticulocytes, thromboelastogram). Opioid analgesics (boluses of Promedol (trimeperidine), Moscow Endocrine Factory, Russia) were administered when the VAS score was > 4 with routine analgesic therapy.

Statistical analysis was performed using Jamovi software (version 2.3.18). The 95% confidence interval (CI) and two-tailed significance level of $P<0.05$ were selected. The Shapiro–Wilk test was chosen to test the normality of the distribution. Pearson's *t*-test and correlation coefficient and nonparametric chi-square test without continuity correction were used to compare the data obtained. For all comparisons described below, except for the VAS score, the Shapiro–Wilk test for normality yielded a value of $P>0.05$, indicating a normal distribution.

Results and Discussion

The first step was to evaluate the effect of preventive use of NSAIDs on the quality of pain relief during surgery. The induction of anesthesia provided a sufficient level of pain relief in both groups, but at the same time the values of the pain measuring device increased until the end of anesthesia. Thus, the qNOX index in the ibuprofen group was 37.5±7.3 at the beginning of surgery and 61.8±8.4 at the end of surgery, while in the ketoprofen group it was 40.6±4.8 and 57.2±9.0, respectively. The difference in values between the stages within each group was significant ($P<0.05$), but no significant difference was found when comparing the groups.

It can be assumed that the prophylactic use of the studied NSAIDs has a similar effect on intraoperative pain severity.

The groups were also compared in terms of postoperative pain intensity. Throughout the follow-up period, VAS scores were lower in the ibuprofen group than in the ketoprofen group.

In the first stage of the postoperative period, the VAS in the ibuprofen group was 2.93±1.53 cm and in the ketoprofen group 4±2.30 cm, $P=0.04$; in the second stage, 2.25±0.86 cm (ibuprofen) and 3.67±1.79 cm (ketoprofen), $P=0.036$; in the third stage, 2.31±1.08 cm and 3.38±1.86 cm, $P=0.044$ (chi-squared test), i.e., the maximum difference was observed in the first hours and averaged 32.4% (Fig. 1). After 9 hours post-surgery, the VAS difference between the groups decreased significantly, with no differences observed only at the end of the first day after surgery.

Correlation analysis was performed to determine the relationship between the VAS score after

the patient awakening and the qNOX score at the end of surgery. The Pearson correlation coefficient was 0.43 (P=0.0007), indicating that the patient's perception of pain in the postoperative period corresponded to the instrumental assessment intraoperatively (Fig. 2).

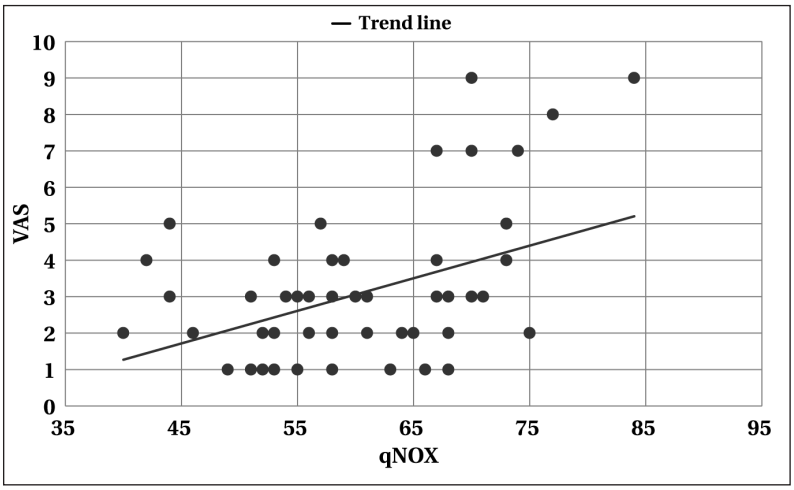

Fig. 2. Pearson's correlation of VAS values after patient awakening and qNOX at the end of surgery.

Ibuprofen and ketoprofen had similar intraoperative analgesic effect, but on admission to the ICU, patients in the ibuprofen group reported a lower intensity of pain syndrome. It seems unlikely that the effect of ketoprofen stops at the moment of anesthesia termination, so the reason for the differences in pain assessment between the groups, most likely, was the individual patient's perception of pain sensation. In other words, ibuprofen probably influences not only the focus of pain, but also its conscious perception by brain.

When assessing the changes in plasma cortisol, no significant intergroup difference was observed: in group 1 its concentration at the end of observation was 571.3±336.8 nmol/L, and in group 2, 402.2±265.0 nmol/L (P=0.105), while the need for opioid analgesics occurred significantly less frequently in the ibuprofen group. Thus, in this group the need for Promedol boluses was observed in 10 out of 32 patients (31%), while in the ketoprofen group, in 17 out of 26 patients (65%). Mean daily drug consumption was assessed only among those patients who received the drug. In group 1, the mean daily requirement for Promedol was 42±17.5 mg versus 50±19.7 mg in group 2; the differences were significant (P=0.022).

The data obtained suggests that while patients' self-rated pain levels appeared to level off by the end of the first day, this was likely due to higher doses of opioid analgesics administered in the second group.

A comparative assessment of the effect of the drugs on the kidneys, based on urea and creatinine levels, showed no statistically significant differences between the groups. The level of cystatin C immediately following surgery was 0.92±0.24 mg/L in the ibuprofen group and 1.17±0.42 mg/L in the ketoprofen group, though the differences between the groups were not significant (P=0.05). However, this parameter exceeded the upper limit of the reference interval in 10 patients (31.3%) in group 1 and 5 patients (19.2%) in group 2.

The level of cystatin C the following morning was 0.95±0.29 mg/L in the ibuprofen group and 1.19±0.43 mg/L in the ketoprofen group (P=0.027). Furthermore, values exceeding the upper reference limit were observed in 14 cases (43.8%) of group 1 and 15 cases (57.8%) of group 2.

An increase in cystatin C levels above normal indicates kidney function impairment. Renal dysfunction was observed in 4 of 32 patients (12.5%) in group 1 and 10 of 26 patients (38.5%) in group 2 from postoperative day to the next morning. The chi-squared value of 0.031 confirmed significant differences between the two groups (P=0.05). The immediate increase in the renal dysfunction marker after surgery reflects the combined negative effects of surgical stress and medication. Despite similar surgical procedures in both groups, the lower incidence of renal dysfunction in the ibuprofen group suggests a safer profile for this drug compared to ketoprofen.

To evaluate blood coagulation, we compared coagulation parameters (fibrinogen, APTT, D-dimer, INR) and thromboelastographic results. We found no significant intergroup differences in both static and dynamic tests, which allows us to assume the absence of any significant effect of the studied drugs on the function of the blood coagulation system with the current regimen of their administration. We also found no effect of both NSAIDs on hematopoiesis (the reticulocyte count did not fall below the reference interval in any patient).

In general, the use of ibuprofen in the perioperative period provided better anesthesia than the use of ketoprofen. However, the authors acknowledge that the lack of a predetermined sample size is a limitation of the study.

Conclusion

Preventive administration of ibuprofen and ketoprofen resulted in a similar analgesic effect during elective surgery under general anesthesia.

We found a statistically significant reduction in the need for additional boluses of opioid analgesics in the group of patients receiving ibuprofen in the postoperative period.

Neither drug had a clinically significant effect on coagulation and hematopoiesis. However, renal dysfunction was less frequent in the ibuprofen group.

Thus, the use of ibuprofen for preemptive analgesia in the perioperative period offers several advantages for pain management.

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