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FAST-TRACK SURGERY PROTOCOLS APPLICATION IN EARLY RECOVERY AFTER SURGERY PRINCIPLE IN THE FIELD OF LAPAROSCOPIC CHOLECYSTECTOMY ANAESTHETIC SUPPORT

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The purpose of the study was to improve the results of laparoscopic cholecystectomy anaesthetic support by the peri- and postoperative analgesia methods optimization. Laparoscopic cholecystectomy was performed in 136 patients with acute cholecystitis. Patients were randomized into 3 groups. The scheme of multimodal analgesia in patients of the 2nd and 3rd groups included paracetamol, dexketoprofen and nefopam with infiltration anaesthesia using bupivacaine and ropivacaine. The data obtained confirm the efficacy of multimodal analgesia regimen using abovementioned remedies in patients undergoing laparoscopic cholecystectomy. Bupivacaine and ropivacaine antinociceptive efficacy while providing infiltration anaesthesia in laparoscopic cholecystectomy dynamics was found to be comparable. The efficacy of the applied multimodal analgesia scheme was confirmed by adequate primary and secondary treatment results and suppression of pain syndrome and postoperative complications. Complex low-opioid anaesthesia during laparoscopic cholecystectomy reduced the use of nonsteroid anti-inflammatory and analgesic remedies during the postoperative period. The authors believed the data obtained is a clinical background for the applied anaesthetic management scheme clinical effects check reasonability during laparoscopic operations in cases of acute gallbladder damage.

Key words: acute cholecystitis, laparoscopic cholecystectomy, anaesthetic support, multimodal anaesthesia, infiltration anaesthesia, postoperative pain, “fast-track surgery”, pathophysiological mechanisms, sanogenetic mechanisms.

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ЗАСТОСУВАННЯ ПРОТОКОЛІВ “FAST-TRACK SURGERY” ДЛЯ РАННЬОГО ВІДНОВЛЕННЯ ПІСЛЯ ОПЕРАЦІЙ СТОСОВНО АНЕСТЕЗІОЛОГІЧНОЇ ПІДТРИМКИ ЛАПАРОСКОПІЧНОЇ ХОЛЕЦИСТЕКТОМІЇ

Метою дослідження було покращення результатів анестезіологічного забезпечення лапароскопічної холецистектомії у пацієнтів шляхом оптимізації методів періопераційного знеболення. Лапароскопічну холецистектомію виконували у 136 хворих на гострий холецистит. Хворі були рандомізовані на 3 групи. До складу мультимодальної аналгезії у хворих 2-ї та 3-їх груп включали парацетамол, декскетопрофен та нефопам із інфільтраційною анестезією бупівакаїном та ропівакаїном. Отримані дані доводять ефективність схеми мультимодальної аналгезії при вживанні вищенаведених препаратів при виконанні лапароскопічної холецистектомії. Антиноцицептивна ефективність розчинів бупівакаїну та ропівакаїну при забезпеченні інфільтраційної анестезії в динаміці лапароскопічної холецистектомії виявилася співставною. Ефективність застосованої схеми мультимодальної аналгезії підтверджена адекватними первинними та вторинними результатами лікування та пригніченням вираженості больового синдрому і післяопераційних ускладнень з боку нервової та вегетативної систем і активності шлунково-кишкового тракту. Застосування комплексної малоопіоїдної анестезії при виконанні лапароскопічної холецистектомії зменшило вживання нестероїдних протизапальних та протибольових фармакологічних препаратів в динамці післяопераційного періоду. Автори вважають отримані дані клінічним підгрунтям доцільності подальшого тестування клінічних ефектів застосованої схеми анестезіологічного менеджменту при лапароскопічних операціях з приводу гострого ураження жовчного міхура.

Ключові слова: гострий холецистит, лапароскопічна холецистектомія, анестезіологічна підтримка, мультимодальна анестезія, інфільтраційна анестезія, післяопераційний біль, “fast-track surgery”, патофізіологічні механізми, саногенетичні механізми.

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Acute cholecystitis (AC) occupies a leading place in the structure of abdominal organs acute surgical diseases, second only to acute appendicitis [4, 5]. An increase in number of patients with gallstone disease (GSD) and AC is observed throughout the world [8]. The incidence rate of GSD in various countries increases in 17–25 % of the adult population [10], and in Ukraine up to 20 % [1] with which the number of patients doubles 10 years [5, 6].

The high diagnostic value of laparoscopy in AC diagnosis and treatment [5], the relative technical simplicity of laparoscopic cholecystectomy (LCE) and less damage of the frontal abdominal wall vs the same in case of open cholecystectomy (OCE) contribute to the fact that most surgeons currently prefer laparoscopic technologies [15]. The LCE advantages include its cheapness since the significant cost of the procedure itself is offset by a shorter duration of inpatient treatment and loss of ability to work [5, 8].

The rapid development of medical and especially surgical and anaesthetic technologies made possible to revise the traditional postulates of surgical patients perioperative management. The first steps directed to patients accelerated recovery after surgical interventions appeared at the end of the XX century. Prof. Henrik Kehlen (Denmark) is the pioneer of the "Fast track surgery" concept [7, 11].

Therefore, a multimodal "Fast-Track Surgery" approach of perioperative management, including nutrition and analgesia was introduced and later transforms into the "Enhanced Recovery After Surgery" (ERAS) program – an evidence-based approach to perioperative care aimed to enhance recovery [2]. The main goals of ERAS are the improvement of surgical outcomes, reduction of complications, improved patient experience and reduction in stay-in duration [12]. ERAS programs have been successfully implemented in different areas of surgery and offer results that justify the growing corpus of publications surrounding this paradigm [7, 12].

Abdominal surgery is known to be the most painful procedures [9], and the subsequent risk of chronic pain and postoperative opioid dependence is apparent [10]. There are significant practice variations across institutions and countries in the treatment and perioperative care of patients with acute abdominal catastrophe, i.e. acute cholecystitis [1, 8, 10]. These differences lead to varied perioperative surgical outcomes, including stay-in duration, postoperative complication rates and rates of functional recovery [5]. Therefore, there is a significant clinical and economic rationale for these clinical conditions outcomes management improvement [12]. The literature studying the application of ERAS protocols in abdominal surgery is still recent [7, 12, 14].

Anaesthetic support for AC operations is of great importance in both immediate and postponed outcomes improvement and in mortality reduction in AC destructive forms and their complications. One should stress that complications of different severity often occur throughput the postoperative period after anaesthesia, i.e., postoperative nausea and vomiting, sedation, dehydration, urinary retention etc. [2]. Important that postoperative pain nature after LCE is complex and indicates that its treatment should be multimodal [10]. Great attention today is attached to minimizing the opioids use in patients treatment during the postoperative period. As an alternative, multimodal analgesia regimens using dexmedetomidine are actively promoted. However, these statements are under intensive discussion [3].

During certain time we used a multimodal analgesia scheme with paracetamol, dexketoprofen, and nefopam hydrochloride in LCE anaesthetic support which efficacy we intend to analyze below.

The purpose of the study was to improve the results of laparoscopic cholecystectomy anaesthetic support by the peri- and postoperative analgesia methods optimization.

Materials and methods. A total of 164 patients with AC, aged 22–61 years (mean age, 56.8±4.8 years), were admitted to the surgical departments of Odessa Regional Clinical Hospital and the Centre for Reconstructive and Restorative Medicine (University Clinic) of Odessa National Medical University between 2021 and 2024.

Clinical conditions of 28 people (17.1 %) were improved after diagnostic measures and conservative symptomatic therapy, and they were removed of the clinical observation. Thus, 136 patients were involved in surgical treatment (73 (55.9 %) – women and 63 – men (44.1 %).

Written consent from patients was obtained to use their treatment results with scientific purposes. The exclusion criteria were: age younger than 22 years and older than 61 years, pregnancy and lactation, patients with obesity and body mass index above 35 kg/m^2, patients with comorbid pathology and individual sensitivity to sedative and anaesthetic drugs, history of opiate addiction. The Charlson Comorbidity Index was calculated for all patients.

After 136 operations started, it was necessary to choose conversion in 6 (4.4 %) cases (2 – at the stage of revision and 4 – at the stage of surgical manipulation) and to finish operation as an OCE. Therefore, 130 LCH operations were performed. All patients were thus randomized into 3 clinical groups.

Anaesthesia in the 1st group (n=48; 23 men and 25 women; mean age 58.2±4.4 years) was performed without opioids. Premedication on the operating table – ondasetron (4 mg intravenously (i.v.)), dexketoprofen (50 mg, i.v.), dexamethasone (4 mg, i.v.); induction of anaesthesia – propofol 1.5-2 mg/kg/hr, i.v.; maintenance of general anaesthesia – sevoflurane, propofol, fentanyl 100 μg every 15-20 min, atracurium besylate (0.3–0.4 mg/kg depending on the required duration of complete neuromuscular blockade).

The multimodal analgesia regimen aor patients in group 2 (n=44; 26 men and 18 women; mean age 56.1±4.3 years) included paracetamol (1000 mg, i.v., drip 30 min before surgery and then every 6 hrs), dexketoprofen (50 mg, i.v., 20 min before surgery and then 50 mg every 12 hrs), nefopam hydrochloride (20 mg, i.v., 20-30 min before the end of surgery and then 20 mg every 8 hrs) as well as infiltration anaesthesia with 0.5 % bupivacaine solution at the port insertion site.

The multimodal analgesia regimen aor patients in group 3 (n=44; 24 men and 20 women; mean age 53.8±4.8 years) included the same remedies and infiltration anaesthesia with 0.5 % ropivacaine solution at the port insertion site. All clinical groups were comparable in terms of gender, anamnestic, anthropometric, laboratory and clinical indexes.

Pain was assessed every 1–2 hrs during 48 hrs after surgery using a 10-point VAPS. Mild pain was defined as a VAPS score from 0 till 4 points. Moderate pain was defined as a VAPS score from 4 till 7 and a severe pain was defined as a VASP score above 7 point in the rest.

The obtained results were statistically analysed using the Bonferroni parametric criterion and nonparametric Kruscal-Wallis criterion for ordinal rough data analysis. The minimum statistical significance threshold was set at $p<0.05$.

Results of the study and their discussion. Among all 136 patients with AC 29 (21.3 %) patients were urgently operated in the acute period of the disease (in the first 72 hrs of AC attack), 91 (66.9 %) patients were operated in the later 72 hrs and 16 (11.8 %) patients were operated urgently because of vital signs due to perforation and peritonitis, regardless the AC attack duration.

136 operations began with a laparoscopic approach, in 6 cases there were a necessity to perform the conversion laparotomy and ended the operation as an OCE. The compartment syndrome, inflammatory infiltrate and damage of the ducts were the causes of conversion laparotomy in 1 case each, in 3 cases – bleeding.

The degree of anaesthetic risk according to American Society of Anaesthesiologists physical status classification was assessed by anaesthesiologist during the initial examination. The majority of patients had complaints on pain localised in right hypochondrium, nausea on admission. According to these indexes as well as to anthropometric data, all groups of clinical observation were comparable (Table 1).

Table 1

Clinical characteristics of laparoscopic cholecystectomy peri- and postoperative period in conditions of the applied anaesthetic scheme

Investigated indexes	Clinical groups		
	Group 1 (n=48)	Group 2 (n=44)	Group 3 (n=44)
Average age, years	58.2±4.4	56.1±4.3	53.8±4.8
Body weight, kg	64.3±5.6	78.2±6.2	72.1±5.8
Body mass index, kg/m^2	28.2±2.6	29.1±3.1	28.8±2.9
Charlson comorbidity index, points	2.3±0.3	2.5±0.3	2.4±0.3
Anaesthetic risk by ASA, I-III, points	29	26	24
Duration of operation, min.	71.6±6.7	68.8±6.3	72.4±6.8
Duration of anesthesia, min	88.3±7.4	81.6±6.7	86.8±7.6
2 hrs after surgery; Pain up to 4 points Pain from 4 till 7points Pain above 7 points	 40 7 1	 43 1* 0	 43 1* 0
12 hrs after surgery; Pain up to 4 points Pain from 4 till 7points Pain above 7 points	 42 5 1	 43 1* 0	 44 0* 0
24 hrs after surgery; Pain up to 4 points Pain from 4 till 7points Pain above 7 points	 44 3 1	 44 0 0	 44 0 0
At time of discharge; Pain up to 4 points Pain from 4 till 7points Pain above 7 points	47 1 0	44 0 0	44 0 0
Number of patients with severe pain	8	1*	1*
Nausea	6	1*	2*
Vomiting	3	0	0
Intraoperational sevoflurane use, ml	8.3±0.7	5.3±0.4#	5.7±0.4#
Intraoperational fentanyl use, mg	0.78±0.06	0.42±0.04#	0.44±0.04#
Total morphine use, mg	15	0*	0*
Duration of awakening after surgery, min.	9.2±0.7	4.4±0.4#	5.2±0.4#
Duration of stay-in, days	3.6±0.3 (3–4)	2.8±0.3 (2–3)	2.6±0.2 (2–3)

Notes: * – $P<0.05$ – statistical differences of the investigated parameters compared with the same in the control group (Kruscal-Wallis criterion); * – $P<0.05$ – statistical differences of the investigated parameters compared with the same in the control group (Bonferroni criterion).

Intraoperatively, we did not observe significant changes in cardiohemodynamics or oxygen saturation in patients from the observed clinical groups that would have affected the course of the surgical intervention. The main homeostatic parameters slight changes, were quickly normalized.

The duration of the operation in patients of all three groups ranged from 64 to 82 min and averaged from 68.8±6.3 min in the 2nd group to 72.4±6.8 min in the 3rd group, which did not reveal a statistical difference ($p>0.05$).

Similarly, the anaesthesia duration was comparable in all groups, the average values of which ranged from 76 to 95 min ($p>0.05$). After the operation all patients were transferred to the hospital wards.

The average expression of moderate pain (up to 4 points) 2 hrs after the operation was registered in the majority of 1–3 groups patients. Severe pain was noted in 7 patients of group 1 (average 5.6±0.5 points), 1 patient in groups 2 and 3 complained on a similar nature of pain which was significantly less compared with this index in group 1 ($p<0.05$). 1 patient in group 1 complained on excessive pain reaction; similar complaints were absent in patients of groups 2 and 3.

Moderate pain was also recorded in the majority of patients in groups 1–3, 12 hrs after surgery. 5 patients in group 1 had severe pain (average 4.9±0.5 points), 1 patient in group 2 complained of a similar nature of pain, which was significantly less than the same index in group 1 ($p<0.05$). And the same patient in group 1 again complained of excessive pain reaction 12 hrs after surgery; similar complaints were absent in patients in groups 2 and 3.

3 patients in group 1 complained of severe pain, and 1 patient complained of excessive pain 24 hrs after surgery. Similar complaints were absent in patients of the 2nd and 3rd groups ($p > 0.05$).

Pain syndrome nature and expression at the time of discharge from the hospital were insignificant, and all three groups were comparable by this index ($p>0.05$). 8 patients in group 1 complained of severe pain during the complete postoperative period. Similar complaints were registered in 1 patient in groups 2 and 3 ($p < 0.05$).

During the postoperative period, 9 patients of the 1st group had complications in the form of nausea (6 patients) and vomiting (3 patients), which exceeded these indexes in patients of the 2nd and 3rd groups, respectively ($p<0.05$).

Sevoflurane and fentanyl intraoperative consumption in patients of groups 2 and 3 was significantly less compared to similar indexes in patients of group 1 (by 46.6–56.6 % and by 77.2–85.7 %), respectively ($p<0.05$). At the same time, patients of groups 2 and 3 did not require the use of morphine during the postoperative period. A major number of patients with complaints on excessive pain in group 1 required 15 mg of morphine in the postoperative period ($p<0.05$).

The duration of awakening after surgery did not differ in the 2nd and 3rd groups but these indexes were half as long as the same ones when performing LCE in patients of the 1st group ($p<0.05$). The stay-in duration, thus, differs insignificantly among all examined groups of patients ($p>0.05$).

Thus, the analysis of the data obtained allowed us to demonstrate several fundamental points. Firstly, we consider important the verified efficacy of the multimodal analgesia scheme consisting of paracetamol, dexketoprofen, and nefopam hydrochloride in patients with LCE. Secondly, the high efficacy, which proved to be comparable, was demonstrated in the case of bupivacaine and ropivacaine used for infiltration anesthesia in patients with LCE.

Thirdly, the efficacy of the applied multimodal analgesia scheme with paracetamol, dexketoprofen and nefopam hydrochloride administration and infiltration anaesthesia using 0.5 % solutions of bupivacaine and ropivacaine during the postoperative period was confirmed by adequate primary (normal indexes of cardiohemodynamics and blood oxygen saturation throughout the intraoperative period) and secondary treatment results and significant pain syndrome suppression together with postoperative complications involved nervous and autonomic systems and gastrointestinal tract.

And, fourthly, we note that complex low-opioid anaesthesia during LCE considerably reduced the use of nonsteroidal anti-inflammatory and analgesic remedies during the postoperative period, which, in addition to a marked antinociceptive effect, indicates in favour of the applied anaesthetic management scheme. Clinical effects, further testing during laparoscopic operations for acute gallbladder lesions is warranted.

To discuss and analyse the results obtained, we will define the following three aspects. First, statistical indexes, unfortunately, declare a gradual increase of GBD and AS incidence and cases of this pathology exacerbation [1, 6], which requires surgeons to constantly improve their diagnostic and therapeutic competencies and skills, and anaesthesiologists to improve and optimize anaesthetic support constantly during the surgical treatment of a specified contingent of patients. Our work is carried out in the appropriate direction, which is natural for specialists in the field of anaesthesia from leading European and world clinics [8, 9, 12].

Secondly, the geriatric risk in abdominal surgery is a worrying factor which poses a rather difficult task for anaesthesiologists to ensure surgical intervention in elderly patients with an expressed compromise of bodies regulatory systems activity and a significant set of comorbidities which limits the anaesthesiologists'

arsenal of actions [1, 6]. Thus, we have good preliminary results which indicate a significant reduction in "rescue analgesics" and morphine use during the postoperative period as well as episodes of vegetative dysfunction [8].

Thirdly, intraoperative use of the original multimodal analgesia scheme with paracetamol, dexketoprofen and nefopam hydrochloride administration and infiltration anesthesia with 0.5 % solutions of bupivacaine and ropivacaine significantly reduced the postoperative pain severity, which intensity suppression is considered to be one of the most important results for patients and has a significant impact on the course of the postoperative period, the time of patient's recovery after surgery and the frequency of complications. We emphasize that pain severity in patients of the 2nd and 3rd groups was minimal throughout the entire postoperative period, and its elimination was also registered faster in the postoperative period dynamics.

There are data on moderate and severe abdominal pain complaints in 35-65 % of patients during the first 48 hrs after LHE [8]. We consider appropriate to note that achieved antinociceptive effect due to original scheme of multimodal anaesthesia and postoperative analgesia use had not only a direct therapeutic "application endpoint" but also initiated, through "vicious circle" and the feedback mechanism, the sanogenetic mechanisms activation with the involvement of biochemical, energetical, endocrine and humoral resources, which generally contributed to number of side effects in the postoperative period reduction and bodies vital organs and systems functional activity fastest and effective restoration. The latter position, and this is the fourth, we consider a very important component of the "Fast track surgery" concept and the |Enhanced Recovery After Surgery" program.

We also want to express our opinion regarding the mechanisms of implementing the clinical effect of the used multimodal LCE anaesthetic support scheme. With paracetamol plus dexketoprofen and nefopam combining, we achieved a complex analgesic, anti-inflammatory, and antipyretic effect due to COX_3 activity suppression by paracetamol [13] and COX_2 – by dexketoprofen [3] with descending serotoninergic neurotransmission stimulation by nefopam [13]. There are data on paracetamol and dexketoprofen comparable anti-inflammatory and analgesic effects [3] but nefopam hydrochloride is principally new "participant" of the original scheme which is fundamentally different from other centrally acting analgesics. Nefopam is well known to inhibit the synaptosomal noradrenaline, dopamine, 5-hydroxytryptophan, and GABA reabsorption and to stimulate dopamine and GABA release in the brain [13]. It does not bind to opioid analgesic receptors and does not inhibited by naloxone. Unlike narcotics, nefopam hydrochloride does not cause respiratory depression [13].

Resuming, we stressed that clinical results obtained regarding the LCE effective anaesthetic support using the original scheme of multimodal analgesia, despite its general antinociceptive focus and anaesthetic efficacy, we consider to be preliminary optimistic but at the same time we state that data obtained further vigilant verification is necessary. The achieved improvement of an organism physiological reserves and vital organs and systems with regulatory mechanisms activation are, in our opinion, the result of sanogenetic mechanisms activation due to complex scheme of multimodal analgesia with postoperative anaesthesia use.

We consider it appropriate to perform clinical observations aimed to analyze the efficacy of anaesthetic scheme we used in OCE, since this disease clinical manifestation complexity and the unpredictability of intra-abdominal phenomena during the operation give a significant percentage of conversion laparotomy episodes in surgical interventions that began laparoscopically. If there are successful results, we hope for, our data will serve as a contribution to "Fast-track surgery" concept of the "Early Recovery After Surgery" program.

Conclusions

1. The efficacy of a multimodal analgesia regimen using paracetamol, dexketoprofen and nefopam hydrochloride was proved in patients with LCE.

2. Bupivacaine and ropivacaine antinociceptive efficacy while providing infiltration anaesthesia in LCE dynamics was found to be comparable.

3. The efficacy of the applied multimodal analgesia scheme with paracetamol, dexketoprofen, and nefopam administration and infiltration anaesthesia with 0.5 % solutions of bupivacaine and ropivacaine in the postoperative period was confirmed by adequate primary and secondary treatment results and pain syndrome with postoperative complications suppression.

4. In conditions of the applied complex scheme of multimodal anaesthesia, normal indexes of cardiohemodynamics and blood oxygen saturation were recorded in patients during LCE throughout the intraoperative period. The period of awakening after anaesthesia was reduced.

5. Complex low-opioid anaesthesia during LCE significantly reduced the use of nonsteroid anti-inflammatory and analgesic remedies during the postoperative period.

6. The positive results obtained we considered as a clinical background for the applied anaesthetic management scheme, clinical effects, and checking reasonability during laparoscopic operations in cases of acute gallbladder damage.

7. If successful, the data we obtained will serve as a contribution to the "Fast-track surgery" concept of the "Early Recovery After Surgery" program.

Prospects for further research are aimed at additional clinical testing of anaesthetic efficacy of the multimodal anaesthesia regimen used for open cholecystectomy and the necessary validation of antinociceptive activity mechanism of implementation in these conditions. An additional direction of research is considered to be a clinical algorithm development for intra- and perioperative pain relief during open and laparoscopic cholecystectomy to reduce the incidence of complications throughout the postoperative period.

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