

NEW ASPECTS IN THE USE OF MULTIMODAL ANALGESIA DURING SURGICAL INTERVENTIONS IN CANCER PATIENTS: A LITERATURE REVIEW

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ABSTRACT

Relevance: Multimodal analgesia is an important tool in postoperative pain management in cancer patients. It provides a comprehensive approach that minimizes side effects, improves recovery, and improves the patient's quality of life in the postoperative period.

The study aimed to generalize current data from systematic reviews, meta-analyses, and randomized controlled trials that consist of strategies and new aspects of multimodal analgesia for oncological surgery. An important aspect is the identification of effective methods for pain management in patients who have undergone surgery due to cancer.

Methods: The Cochrane Library, PubMed, and Embase were searched to identify randomized controlled trials, systematic reviews, and meta-analyses published in English from 2019 to 2024 that focused on the results of the use and comparison of different methods of multimodal analgesia during surgical interventions in patients with cancer.

Results: As a result of the analysis of data from large scientific studies and meta-analyses, the advantage of opioid-sparing methods in multimodal analgesia was established, as well as the widespread use of ultrasound-guided peripheral blocks.

Conclusion: A multimodal standardized method of pain relief with ropivacaine (regional blocks) in combination with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) has the best analgesic effect in patients undergoing surgery for cancer and can effectively inhibit early postoperative inflammatory reactions and promote postoperative recovery without increasing the incidence of adverse reactions and complications.

Keywords: multimodal analgesia, patients with cancer, ultrasound-guided regional blockades.

Introduction: Historically, surgical pain (both intra-operative and postoperative) has been treated primarily with strong opioid regimens. Opioids are effective in reducing pain but have undesirable side effects in this patient population, the most important of which is respiratory depression. Other side effects include sedation, altered mental status, constipation, postoperative nausea, vomiting, urinary retention, and pruritus. The clinical significance of these side effects varies from person to person, but opioid side effects hinder the ultimate goal of accelerating the recovery pathway, namely, faster recovery from surgery and return to baseline functional status. Regardless of the complexity of the surgical procedures (major or minor), postoperative opioid administration can result in persistent or chronic opioid use in 5% to 15% of patients, depending on the duration of initial postoperative opioid use [1].

For this reason, enhanced recovery pathways (for any surgical specialty, including thoracic and breast surgeries) tend to use multimodal analgesic regimens that are opioid-sparing in combination with regional techniques such as interfascial blocks when possible [2-3].

The classes of drugs that can be used for perioperative analgesia in a multimodal approach are diverse and include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, NA receptor antagonists, glucocorticoids, and alpha-receptor antagonists. The 2019 Enhanced Recovery After Surgery (ERAS) Society guidelines detailed the perioperative analgesics used and the available data for several drug classes. They made a "strong" recommendation to include acetaminophen/NSAID combination, ketamine and dexamethasone, and paravertebral block as multimodal analgesia [4].

The study aimed to generalize current data from systematic reviews, meta-analyses, and randomized controlled trials that consist of strategies and new aspects of multimodal analgesia for oncological surgery. An important aspect is the identification of effective methods for pain management in patients who have undergone surgery due to cancer.

Materials and methods: The Cochrane Library, PubMed, and Embase electronic database were searched to identify randomized controlled trials, systematic reviews, and meta-analyses published in English from 2019

to 2024 that focused on the results of using and comparing different methods of multimodal analgesia during surgical interventions in patients with cancer. The exclusion criteria were RCTs and systematic reviews, meta-analyses, and sci-

entific articles on the use of multimodal analgesia in pregnant women and children with cancer.

Results: Studies that reflect new aspects of multimodal analgesia are presented in Table 1.

Table 1 – Effectiveness of interfascial blockades in various surgical interventions in patients with oncological diseases

Authors	Year of publication	Type of Research	Cohort	Key Results
Mian BM et al. [1]	2023	Cohort study	N=686	Efficacy of non-opioid alternative methods of multimodal analgesia
Genc C. et al. [2]	2022	RCT	N=90	Equal effectiveness of blockade (fascia of the erector spinae, fascia of the pectoralis, and serratus muscles) and opioid analgesics
Edwards JT et al. [5]	2021	RCT	N=64	30% reduction in 24-hour opioid consumption following serratus interfascial block following mastectomy
Kaur U. et al. [6]	2020	RCT	N=55	Dynamic and static pain relief after blockades (muscles, erector spinae, pectoralis fascia, and serratus)
Sotome S. et al. [7]	2021	RCT	N=45	Erector spinae fascia block is equivalent to but not superior to retrolaminar block for postoperative analgesia after breast surgery.
Yao Y. et al. [8]	2019	RCT	N=68	Serratus fascia block improved the quality of recovery and postoperative analgesia in breast cancer.
Kitagawa H. et al. [9]	2024	RCT	N=64	Multimodal analgesia combined with transversus abdominis fascia block may be comparable to epidural analgesia after laparoscopic colon cancer surgery.
Kuniyoshi H. et al. [10]	2019	RCT	N=100	A case-based rectus block may be a substitute when a continuous epidural block is contraindicated as a component of postoperative multimodal analgesia.
Ma Y. et al. [11]	2024	RCT	N=72	Multimodal opioid-sparing anesthesia may be a safer and more effective alternative to anesthesia in elderly patients, minimizing opioid-related side effects.
Yeo J. et al. [12]	2022	RCT	N=97	Multimodal analgesia (pregabalin + transversus abdominis fascia block + tramadol) successfully controlled postoperative pain and was non-inferior to morphine-based patient-controlled analgesia.
Toleska M. et al. [13]	2023	RCT	N=60	Patients in the opioid-sparing group had the lowest pain scores in the first 72 hours after open colorectal surgery.
Huang D. et al. [14]	2020	RCT	N=77	Bilateral posteromedial quadratus dorsi fascia block reduces morphine consumption in the setting of multimodal analgesia compared with lateral transversus abdominis fascia block after laparoscopic colorectal surgery.
Liang M. et al. [15]	2021	RCT	N=78	Postoperative ultrasound-guided posterior transversalis fascia block with rectus abdominis fascia block reduced postoperative opioid use in patients after laparoscopic radical resection of rectal cancer.
Shi R. et al. [16]	2024	RCT	N=67	Preoperative bilateral quadratus dorsi fascia block reduces postoperative morphine use.
Cao L. et al. [17]	2024	RCT	N= 84	Multimodal standardized analgesia with ropivacaine in combination with parecoxib sodium and a patient-controlled analgesia pump had a better analgesic effect.
Li X. et al. [19]	2021	RCT	N=96	In patients undergoing laparoscopic renal surgery, a preoperative single quadratus dorsi fascia block did not reduce opioid consumption but improved analgesia for up to 24 hours postoperatively.
Zhang Q. et al. [20]	2023	RCT	N=80	Non-opioid anesthesia based on thoracic paravertebral block improved the quality of early postoperative recovery in patients undergoing breast cancer surgery.
Cheneseau J. et al. [21]	2023	RCT	N=196	Surgeon-delivered paravertebral block during thoracoscopy was non-inferior to anesthesiologist-delivered paravertebral block using ultrasound in terms of opioid consumption during the first 48 hours.
De Cassai A. et al. [31]	2021	Meta-analysis	N=4074	All regional block techniques (serratus fascia, pectoralis fascia, and serratus fascia) were associated with superior analgesia and lower opioid consumption than controls.
Ahlberg H. et al. [32]	2023	RCT	N=185	Combined pectoralis fascia and serratus block before breast cancer surgery reduces postoperative morphine requirements.

A review of included meta-analyses, systematic reviews, and RCTs showed that, with advances in technology, including ultrasound (US), regional blocks had become an integral part of multimodal analgesia in oncologic surgery, and are associated with less pain, less postoperative nausea and vomiting, and shorter hospital stays in patients undergoing thoracic, urologic, and breast surgery [5-7].

An RCT by Yao et al. examined the use of ultrasound-guided serratus plane block (SPB) for pain relief after breast cancer surgery. According to the 40-item Quality of Recovery questionnaire, the global median

score at 24 hours after surgery was significantly higher in the SPB group (158 [153.8-159.3]) than in the placebo (saline) control group (141 [139-145.3]), with a mean difference of 15 (95% CI: 13 to 17, $p<0.001$) (Table 2) [8].

Compared with the control group, postoperative pain scores (assessed by visual analog scale) at rest were significantly lower at 24 hours in the SPB group ($P<0.001$) (Figure 1).

Preoperative SPB reduced postoperative total opioid consumption, incidence of postoperative nausea and vomiting, and time to discharge from the anesthesia

care unit. In addition, patient satisfaction scores were higher in the SPB group.

Although continuous epidural analgesia remains the standard method and part of multimodal perioperative analgesia, recent advances in ultrasound devices allow good visualization of block needles, thereby facilitating

the placement of catheters in appropriate positions for continuous peripheral nerve blocks in the perioperative period. In cases where epidural analgesia is contraindicated, continuous plane blocks can be considered as an alternative to epidural analgesia for adequate pain management [9].

Table 2 – 40-item Postoperative Quality of Recovery Questionnaire, 24-hour global assessment [8]

Variables	Serratus muscle block, n=34	Control group, n=34	Median difference (95% CI)	Probability value
Global Quality of Recovery Questionnaire – 40 items	158[153.8 to 159.3]	141[139 to 145.3]	15[13 to 17]	<0.001
Emotional status	31[28.8 to 33]	28[27 to 29]	3[2 to 4]	<0.001
Physical comfort	50[49 to 51]	43.5[42 to 46]	6[5 to 8]	<0.001
Physical independence	14[12.8 to 16]	13[12 to 15]	1[0 to 2]	0.168
Psychological support	28[29 to 30]	28[26 to 29]	1[0 to 2]	0.061
Pain	33[32 to 34]	28[27 to 30]	4[4 to 5]	<0.001

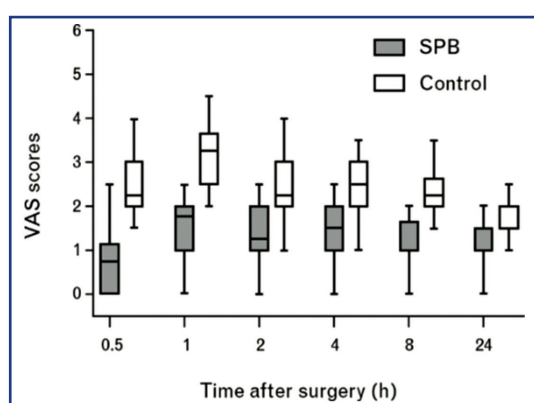


Figure 1 – Box plot of postoperative visual analog scale at rest in patients receiving serratus muscle block (SPB) with 0.5% ropivacaine compared to saline [8]

In an RCT comparing the results of continuous epidural analgesia (CEA) and continuous rectus sheath block (CRSB) conducted by H. Kuniyoshi et al., the post-

operative mean pain score in the CEA and CRSB groups during movement and rest was less than three during the observation period (Figure 2) [10].

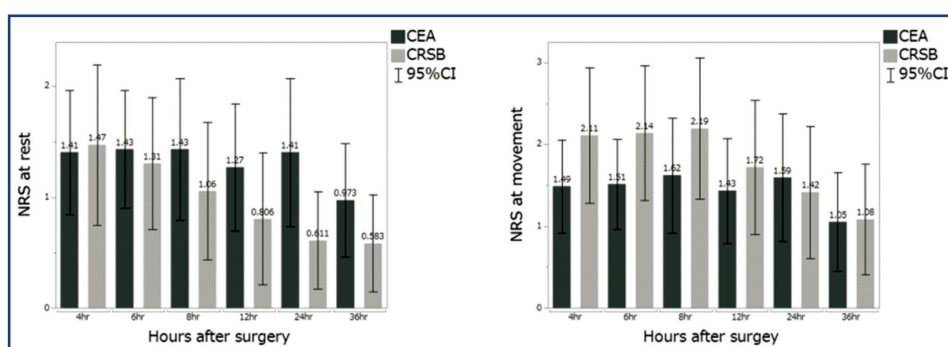


Figure 2 – Postoperative Numeric Rating Scale in the Continuous Epidural Analgesia (CEA) Group and the Continuous Rectus Spinal Block (CRSB) Group at Movement and Rest. Data are presented as mean and 95% CI [10]

There was no significant difference between the groups in the need for intravenous patient-controlled analgesia (IV-PCA), the total number of IV-PCA requests, and the frequency of rescue medications. Rescue analgesics included NSAIDs, acetaminophen, and buprenorphine. Ta-

ble 3 shows no significant difference between the CEA and CRSB groups concerning rescue medications [10].

Planar regional blocks performed under ultrasound control have become widespread in combination with perioperative multimodal analgesia in other areas of

oncological surgery, including urological and abdominal operations [11-13].

According to the ERAS guidelines, various analgesic methods are recommended for minimally invasive colorectal surgery, such as intravenous patient-controlled

analgesia (IV-PCA) in combination with acetaminophen, NSAIDs, or opioid agonists, as well as incisional wound infiltration with local anesthetics, transverse abdominis plane block, ultrasound-guided rectus abdominis compartment block, or other analgesic methods [14-17].

Table 3 – Duration, overall frequency, frequency of success, frequency of failure of rescue drugs [10]*

	Extended epidural analgesia	Extended rectus abdominis block	Meaning probabilities
Duration of intravenous patient-controlled analgesia (min)	2040 (1560-2460)	2310 (1515-2760)	0.50
The overall frequency of use of intravenous patient-controlled analgesia	30 (8.5. 49.5)	22 (4-68)	0.83
The success rate of intravenous patient-controlled analgesia	14 (7.5-24)	11.5 (4-24.75)	0.53
Incidence of failure of intravenous patient-controlled analgesia	13 (1.5 32.5)	8.5 (1-42.75)	0.97
Frequency of use of rescue medications (NSAIDs, acetaminophen, and buprenorphine)	2 (0-4.5)	1 (0-3.75)	0.54

Note: *Data are presented as median (quartile range)

Despite the advent of laparoscopic and robotic surgery, open colectomy continues to be performed worldwide. Such procedures are associated with significant postoperative pain. In 2016, the PROSPECT task force proposed recommendations based on a systematic review of 93 randomized controlled trials (RCTs) on pain relief after open colectomy. Following registration on PROSPERO (CRD4202338800), a systematic review of the literature on analgesia after open colectomy was conducted according to the PROSPECT methodology. Embase, MEDLINE, and Cochrane databases were searched specifically for this study for RCTs published between 1 January 2016 and 1 January 2022. The analgesic regimen for open colectomy should include intraoperative paracetamol and specific COX-2 inhibitors or NSAIDs (colon surgery only), epidural anesthesia, and continued analgesia in the postoperative period using opioids as rescue analgesics. If epidural anesthesia is not possible, bilateral TAP block or intravenous lidocaine is recommended. Safety issues should be emphasized: local anesthetics should not be administered via two different routes simultaneously. Careful dosing and monitoring are necessary due to the risk of toxicity [18].

An RCT by Li et al. shows that quadratus lumborum block (QLB) is one of the modern methods of regional anesthesia that is used to control pain, both somatic and visceral, in the abdominal area, including the lateral and anterior parts, during urological surgeries.

Compared with the control group, postoperative somatic pain scores at both rest and cough were significantly lower in the group of patients who received QLB block via the lateral approach (at rest, median difference -1, $P<0.001$; during cough, median difference -2 to -1, $P<0.001$) and in patients who received QLB block via the posterior approach (at rest, median difference -1, $P<0.001$; during cough, median difference -2 to -1, $P<0.001$) (Figure 3) [19].

The use of opioids in the perioperative period is associated with increased postoperative nausea and vomiting, hyperalgesia and chronic pain after surgery, and a variety of other adverse events, particularly relevant

in the recovery of patients who have undergone breast cancer surgery. In an RCT by Zhang et al., the quality of recovery of patients after breast cancer surgery according to the QoR-15 (15-item Quality of Recovery) scale was 100% among 40 patients who underwent multimodal analgesia without opioids (NSAIDs + ultrasound-guided paravertebral block), and 82.5% among 40 patients in the control group ($P=0.012$) (Figure 4) [20].

However, even if US-guided paravertebral block is a reliable method, failure of pain control is a common problem due to technical problems and insufficient personnel training, and therefore, the procedure fails in 6-10% of cases. Thus, paravertebral block with video-assisted thoracoscopy-VATS in patients undergoing lung tumor surgery may be an option with the advantages of thoracoscopic direct visualization of the pleural cavity, ensuring correct intercostal space definition and insertion depth, especially in overweight patients with poor echogenicity of US images. Pain scores on the visual analog scale at rest and with cough at 4, 6, 12, and 48 hours after PVB were similar in the two groups (Figure 5) [21].

A systematic review by BC Go et al. comparing multimodal analgesia with a control group (a total of 10 studies involving 1253 patients (multimodal analgesia group, $n=594$; control group, $n=659$)) found that gabapentinoids were the most commonly used drugs (72.9%), followed by NSAIDs (44.6%), acetaminophen (44.3%), corticosteroids (25.1%), ketamine (7.2%), and nerve blocks (3.4%). Eight studies reported a significant reduction in postoperative opioid use in the multimodal analgesia groups [23]. A meta-analysis by CC Chang et al. found a 46% reduction in the incidence of chronic postoperative pain compared with acute pain after breast cancer surgery (95% CI: 0.25-0.85) [24]. Also, the combination of perioperative oral pregabalin and postoperative S-ketamine effectively prevented chronic pain after breast cancer surgery and reduced acute postoperative pain. It decreased postoperative opioid consumption, although, according to the authors, the data obtained were not analyzed in sufficient detail and require larger-scale studies [25-27].

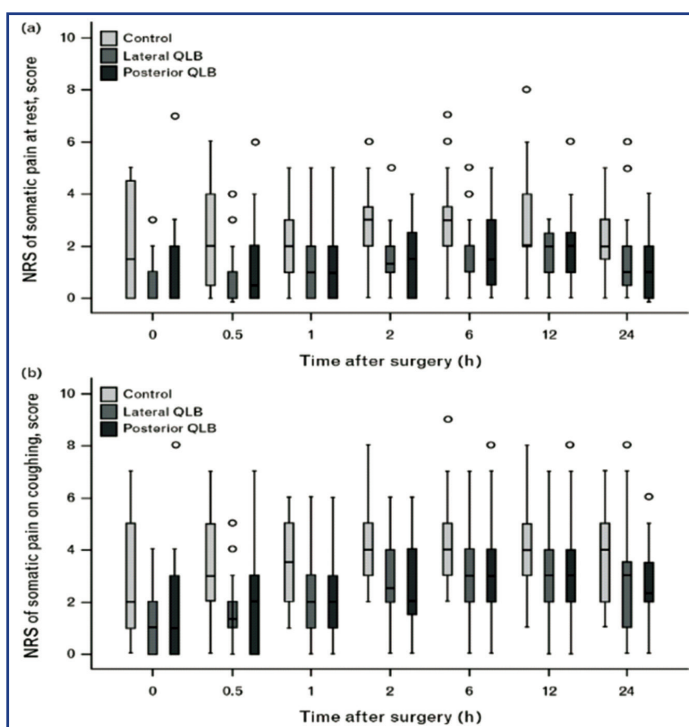


Figure 3 – Numerical rating scale for assessing somatic pain and visceral pain during the first 24 hours after surgery [19]

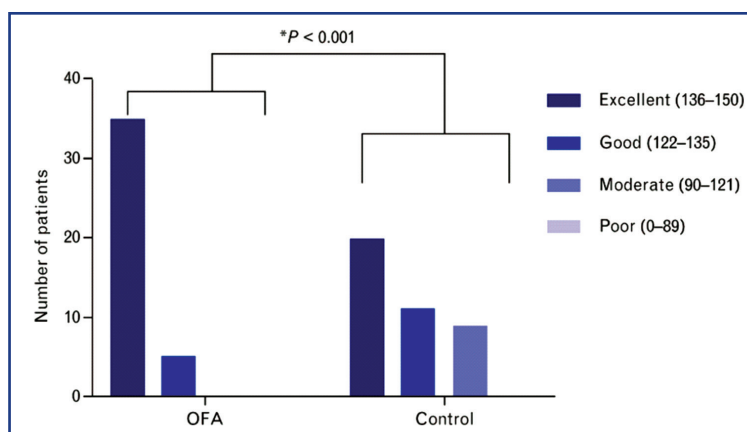


Figure 4 – Distribution of patients by categories of quality of recovery after surgery [20]

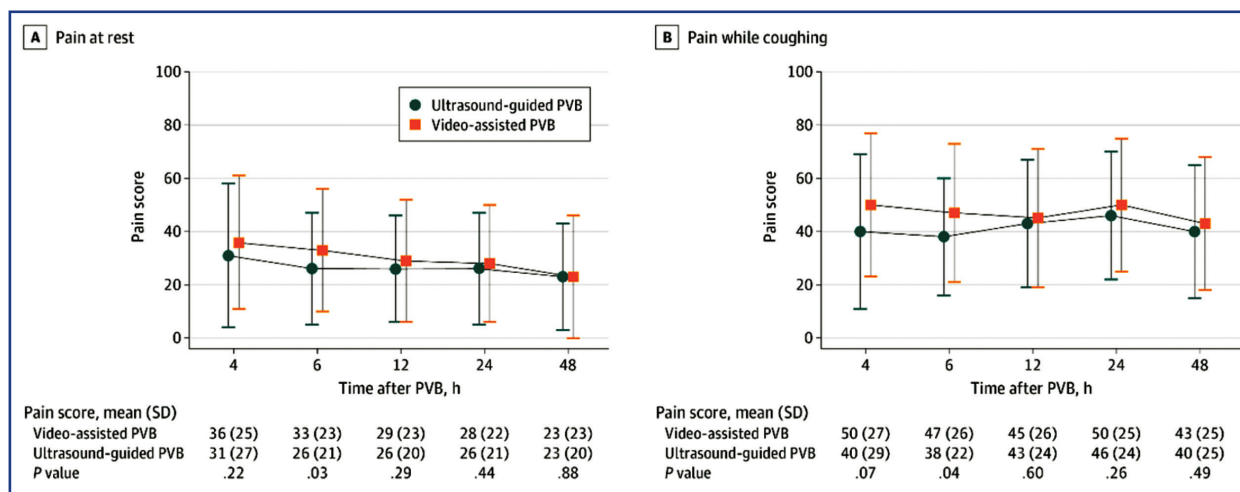


Figure 5 – Postoperative pain according to a visual analog scale at rest (A) and with cough (B) at 4, 6, 12, 24, and 48 hours after video-assisted paravertebral block (VAPV) compared with ultrasound-guided VAPV [21]

Treatment of postoperative pain after head and neck cancer surgery is also a complex issue, along with other oncological diseases, requiring a careful balance between the analgesic properties and side effects of analgesic drugs [22].

In recent years, intravenous lidocaine has become part of opioid-sparing multimodal analgesia protocols, and Wallon et al. conducted an RCT to assess morphine requirements during the first 48 postoperative hours after intraoperative lidocaine infusion during major head and neck cancer surgery involving 118 patients (lidocaine $n = 57$; placebo $n = 61$). No significant difference in morphine consumption during the first 48 hours after surgery was observed in the lidocaine group compared with the placebo group [28].

Discussion: Multimodal analgesia is a combination of different pain relief methods that affect different mechanisms of the pain process. In oncosurgery, multimodal analgesia is used to minimize pain syndrome and reduce the need for opioids, which can cause several undesirable side effects, such as addiction, respiratory depression, and nausea.

Interfascial blocks (e.g., intercostal block of the fascia between the pectoralis major and minor muscles) are an important component of multimodal analgesia, allowing effective pain control, especially in the chest area after chest surgery [29].

In Russian and foreign literature, various techniques of interfascial blockades are described, such as paravertebral blockades for patients with oncological diseases of the chest, which have been proven to be highly effective in reducing postoperative pain syndrome and improving the general condition of patients.

A.Yu. Morunova et al. compared the effectiveness of interfascial erector spine plane (ESP)-block and CEA since these methods not only effectively control pain but also reduce the intensity of surgical stress, which can affect the levels of stress markers, such as cortisol and interleukin-6 (IL-6). The study revealed that the cortisol level in patients receiving ESP-block and CEA was within the normal range during surgery. A day later, the cortisol level statistically significantly decreased in ESP-block patients. On the 3rd day after surgery, a moderate increase in cortisol levels was noted in patients of both groups. In patients of the control group, who underwent general anesthesia without regional pain relief techniques, the IL-6 level during surgery was highest ($p=0.012$). A day after surgery, the highest IL-6 levels were observed in patients in the ESP-block group. The need for opioid analgesics was statistically significantly higher in patients in the control group ($p=0.004$). Adverse events in the form of urinary retention were recorded in 2 (6%) patients in the CEA group [30].

Conclusion: Interfascial blockades have proven to be an important component of anesthetic manage-

ment, especially in minimizing postoperative pain and accelerating recovery. In particular, in the context of laparoscopic surgeries, where the impact on tissues is minimal, but patients may experience significant pain after the intervention, interfascial regional blockades can significantly reduce the need for opioid analgesics, which reduces the risk of side effects and complications [31-32].

The introduction of these blocks into multimodal analgesia, especially in the context of the ERAS protocol, aims to improve the postoperative recovery of patients, which is especially important for cancer patients who may experience more severe postoperative morbidity.

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АНДАТПА

ОНКОЛОГИЯЛЫҚ НАУҚАСТАРҒА ХИРУРГИЯЛЫҚ ОТА ЖАСАУ КЕЗІНДЕ МУЛЬТИМОДАЛДЫ АНАЛЬГЕЗИЯНЫ ҚОЛДАНУДЫҢ ЖАҢА АСПЕКТІЛЕРІ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Өзектілігі: Мультимодальды анальгезия онкологиялық науқастарда операциядан кейінгі ауырсынуды басқарудың маңызды құралы болып табылады. Ол жанама әсерлерді азайтатын, қалпына келтіруді жақсартатын және операциядан кейінгі кезеңде пациенттің өмір сүру сапасын жақсартатын кешенді тәсілді ұсынады.

Зерттеудің мақсаты: Онкологиялық хирургия үшін мультимодальды анальгезиядағы стратегиялар мен жаңа аспектілерді қарастыратын жүйелі шолулардан, мета-талдаулардан және рандомизацияланған бақыланатын сынақтардан ағымдағы дәлелдемелерді біріктіру. Маңызды аспект – қатерлі ісікке байланысты операция жасалған науқастарда ауырсынуды емдеудің тиімді әдістерін анықтау.

Әдістері: Қатерлі ісікке шалдыққан науқастарға хирургиялық ота жасау кезінде мультимодальды анальгезияның әртүрлі әдістерін қолдану және салыстыру нәтижелеріне бағытталған рандомизацияланған бақыланатын сынақтар Cochrane Library, PubMed, Embase электронды базасында 2019-2024 жылдар аралығында ағылшын тілінде жарияланған жүйелі шолулар мен мета-талдауларды анықтау үшін іздестірілді.

Нәтижелері: Ірі ғылыми зерттеулер мен мета-анализдердің деректерін талдау нәтижесінде мультимодальды анальгезияда опиоидты сақтау әдістерінің артықшылығы, сондай-ақ ультрадыбыстық басқарылатын перифериялық блокадаларды кеңінен қолданылуы анықталды.

Қорытынды: Ацетаминофенмен және стероид емес қабынуға қарсы препараттармен (КҚСП) біріктірілген ропивакаинмен (аймақтық блокадалар) ауыруды басудың мультимодальды стандартталған әдісі қатерлі ісікке хирургиялық операция жасалған науқастарда анальгетикалық әсерге ие және операциядан кейінгі ерте қабыну реакцияларын тиімді тежей алады және жағымсыз реакциялар мен асқынулардың жиілігін арттырмай, операциядан кейінгі қалпына келтіруге ықпал ете алады.

Түйінді сөздер: мультимодальды анальгезия, қатерлі ісікпен ауыратын науқастар, ультрадыбыстық бақылаумен жасалынатын аймақтық блокадалар.

АННОТАЦИЯ

НОВЫЕ АСПЕКТЫ ПРИМЕНЕНИЯ МУЛЬТИМОДАЛЬНОЙ АНАЛЬГЕЗИИ ПРИ ОПЕРАТИВНЫХ ВМЕШАТЕЛЬСТВАХ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: Мультимодальная анальгезия является важным инструментом в послеоперационном управлении болью у онкологических пациентов. Она обеспечивает комплексный подход, который минимизирует побочные эффекты, улучшает восстановление и повышает качество жизни пациента в послеоперационном периоде.

Цель исследования – обобщение актуальных данных из систематических обзоров, мета-анализов и рандомизированных контролируемых исследований, которые касаются стратегии и новых аспектов в мультимодальной анальгезии при онкологических оперативных вмешательствах. Важным аспектом данной работы является выявление эффективных методов управления болевым синдромом у пациентов, перенесших операцию на фоне онкологического заболевания.

Методы: Был проведен поиск в электронных базах данных Cochrane Library, PubMed, Embase для выявления рандомизированных контролируемых исследований, систематических обзоров и мета-анализов, опубликованных на английском

языке с 2019 по 2024 годы, в которых основное внимание уделялось результатам применения и сравнения различных методов мультимодальной анальгезии при оперативных вмешательствах у пациентов с онкологическими заболеваниями.

Результаты: В результате анализа данных крупных научных исследований и мета-анализов было установлено преимущество опиоид-сберегающих методов в рамках мультимодальной анальгезии, а также широкое распространение применения периферических блокад, проводимых под ультразвуковым контролем.

Заключение: Мультимодальный стандартизированный метод обезболивания ропивакасином (регионарные блокады) в сочетании с ацетаминофеном и нестероидными противовоспалительными препаратами (НПВП) оказывает лучший анальгезирующий эффект на пациентов, перенесших оперативные вмешательства по поводу онкологических заболеваний и может эффективно ингибировать ранние послеоперационные воспалительные реакции и способствовать послеоперационному восстановлению без увеличения частоты побочных реакций и осложнений.

Ключевые слова: мультимодальная анальгезия, пациенты с онкологическими заболеваниями, регионарные блокады под УЗ-контролем.

Transparency of the study: The authors are solely responsible for the content of this paper.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financing: The authors declare no funding for this study.

Authors' input: contribution to the concept - A.A. Arynov, V.V. Chursin; scientific design – A.I. Abdrakhmanova; execution of the declared scientific research – A.A. Abildaeva, E.A. Seidalieva; interpretation of the stated scientific research – V.V. Chursin; creation of a scientific article – A.A. Arynov, A.I. Abdrakhmanova, A.A. Abildaeva, E.A. Seidalieva, V.V. Chursin.

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