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Comparison of combined general anesthesia with and without epidural morphine on the background of redox therapy in cancer patients with multiorgan resections

Abstract. Background. There are insufficient data on postoperative epidural anesthesia using morphine and conducting redox therapy in cancer patients with multiorgan resections with the assessment of immunological parameters. This work studies the intraoperative use of epidural morphine as compared with combined general epidural anesthesia, as well as the redox therapy in cancer patients with multiorgan resections with an evaluation of the indicators of immunity to provide anesthesia with advanced therapy of possible complications and obtain a more comfortable condition of patients. **Materials and methods.** The study examined 117 cancer patients with locally advanced tumor process of the gastrointestinal tract with multiorgan surgical interventions for health reasons (67.6 ± 3.7 years old). All patients were divided into four groups according to the type of anesthesia and type of antioxidant therapy. The groups with intraoperative epidural morphine use and without it were distinguished. L-ornithine L-aspartate with quercetin complex with povidone was used as an antioxidant therapy. The overall health-related quality of life was evaluated using the standard Short Health Status Assessment Questionnaire SF-36, using the evidence-based methodology. **Results.** The results suggest that in the group using epidural morphine, the degree of anesthesia effectiveness was sufficient, but there were registered the complications, including in the form of apnea while using morphine and a slight deterioration in immunity parameters. When applying the redox therapy, we have achieved improvement both in quality of life and more significantly in immunity. **Conclusions.** Thus, combined epidural anesthesia without morphine against the background of correction of redox metabolism in cancer patients with multiorgan resections is more comfortable for patients, less dangerous due to the lack of development of apnea, psychoemotional and economically justified, which indicates its priority using.

Keywords: epidural morphine; redox therapy; multiorgan resections; combined general epidural anesthesia

Introduction

Every year more than 3.4 million people die worldwide [1]. Gastrointestinal cancer is one of the most frequent causes of cancer deaths in Europe. Non-standard extended and combined interventions performed on several organs using the latest technologies and performing cyto-reduction have become everyday surgical practices [2].

Besides, severe postoperative pain also contributes to the complications associated with immobility, such as, for example, deep vein thrombosis, and this further leads to a delay in discharge of a patient from the hospital [3].

The effect of a single dose of morphine in the epidural space lasts for about a day, often with minor

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symptoms of itching, nausea, vomiting and respiratory depression [4, 5]. Therefore, to date, in cancer patients during multiorgan resections, an important problem is the selection of postoperative analgesia with the most effective analgesic effect, at the same time being safe and comfortable for the patient. Considering the presence of a good analgesic effect of epidural morphine, we supposed to study its safety, its effect on the immune system, and the severity of side effects. It should be noted that studies of immunity in the application of morphine are reflected in many modern studies [6]. The concentrations of IgA and CD3+ reflect the degree of tissue injury, so their release is the lowest with less invasive and traumatic procedures.

Considering that according to the literature data multiorgan surgical interventions are carried out with the most radical removal of healthy tissue, we need to reduce the further complications to ensure the most favorable preparation for the patient with perioperative therapy [7].

As for the prognosis of cancer, according to literature data, the use and priority of the choice of anesthesia can be associated with indicators of cellular and humoral immunity [8, 9].

The correct choice of perioperative management of cancer patients will reduce overall medical costs, accelerate its recovery, provide benefits in psychosocial rehabilitation of patients and provide economic benefits [10].

Epidural anesthesia is often used simultaneously with general anesthesia using inhaled anesthetics or propofol [11, 12], which leads to a decrease in the stress response.

According to the literature data, redox homeostasis and markers of systemic chronic inflammation are disturbed during the formation of oxidative stress [13, 14]. In this case, their laboratory control is important for all conditions accompanied by intoxication and the development of stress in the body. Therefore, when conducting multiorgan resections in cancer patients, it is very important to study the correction of the disorders using perioperative therapy [15]. In our study, we used the introduction of L-ornithine L-aspartate with quercetin complex with povidone.

Our goal was to study the effectiveness of postoperative analgesia in the early return of normal intestinal activity, movement and monitoring of respiratory disorders when using epidural morphine.

Therefore, the study of intraoperative use of morphine with combined general epidural anesthesia is of particular importance. It is also necessary to further study the effect of redox therapy on cellular and humoral immunity in cancer patients with multiorgan resections to ensure anesthesia with advanced therapy of possible complications and to obtain a more comfortable condition of patients.

Purpose: this work studies the intraoperative use of epidural morphine as compared with combined general epidural anesthesia, as well as carrying out redox

therapy in cancer patients with multiorgan resections with an evaluation of the indicators of immunity to provide anesthesia with advanced therapy of possible complications and obtain a more comfortable condition of patients.

Materials and methods

After receiving the approval of the Ethics Committee and informed consent, a prospective, randomized, double-blind study was conducted at the clinical base of the SI "Grigoriev Institute for Medical Radiology of National Academy of Medical Sciences of Ukraine". The study examined 117 cancer patients with locally advanced tumor process of the gastrointestinal tract with multiorgan surgical interventions for health reasons (67.6 ± 3.7 years old). All patients were divided into four groups according to the type of anesthesia and type of antioxidant therapy: I — a group of patients ($n = 25$, group A) undergoing combined general anesthesia with epidural morphine analgesia according to standard protocols, in which antioxidant agents had not previously been used; II — a group of patients ($n = 27$, group B) undergoing combined general anesthesia with epidural analgesia without morphine according to standard protocols, in which antioxidant agents had not previously been used; III — a group of patients ($n = 31$, group C) undergoing combined general anesthesia with epidural morphine analgesia according to standard protocols, who received antioxidant protection with L-ornithine L-aspartate (5 mg/10 ml, 10 ml twice a day, intravenous drip per 500 ml of saline) with quercetin complex with povidone (lyophilisate for a solution of 0.5 g once a day intravenous drip per 100 ml of saline); IV — a group of patients ($n = 34$, group D) undergoing combined general anesthesia with epidural analgesia without morphine according to standard protocols, who received antioxidant protection with L-ornithine L-aspartate (5 mg/10 ml, 10 ml twice a day, intravenous drip per 500 ml of saline) with quercetin complex with povidone (lyophilisate for a solution of 0.5 g once a day intravenous drip per 100 ml of saline).

The physical parameters of the patients: the status of the American Society of Anesthesiologists from II to III, body weight 78.8 ± 2.2 kg, body mass index 27.2 ± 0.9 kg/m². Vital parameters were continuously monitored (electrocardiogram, pulse oximetry (SpO₂) and non-invasive blood pressure measurement (systolic and diastolic)). In addition to general clinical studies, SpO₂ monitoring was performed on the CX100 pulsoximeter and pO₂ and pCO₂ were determined on the ABL80 blood gas analyzer.

All patients were pre-medicated with 0.005–0.008 mg/kg atropine and 0.5–1.0 mg intravascular. The epidural catheter was slowly injected (4–5 ml every 2–3 min) with puncture under local analgesia (2 ml of 2% lidocaine) into the epidural space at the level of Th7–Th8 immediately before induction into general anesthesia with local anesthetic bupivacaine 0.5% at a dose of 15–20 ml. Every 2.5 hours from the start of sur-

gery, bupivacaine 0.5% was injected into the epidural catheter at a dose of 4–5 ml.

For general anesthesia, there was intravenously administered sodium thiopental 4–6 mg/kg or diprofol 1.6–2 mg/kg, midazolam 0.1–0.2 mg/kg. The patients received myorelaxation with a nondepolarizing muscle relaxant of average duration atracurium besylate at a dose of 0.5–0.6 mg/kg. Tracheal intubation was performed, after which maintenance doses of sodium thiopental of 1.5–2 mg/kg or diprofol 0.5–0.8 mg/kg every 20 minutes and atracurium besylate 0.26 mg/kg every 40 minutes were administered. The intraoperative depth of anesthesia was monitored using the Bispectral Index Scale (BIS-A-2000, Aspect Medical Systems, Newton, MA, USA). Every increase in the bispectral index score above 55 or increase in the mean arterial blood pressure or heart rate above 15 % of baseline was followed by a bolus of fentanyl 1 µg/kg IBW and an increase in the continuous infusion rate of fentanyl from 0.1 to 1 µg/kg IBW/min. No other opioids were administered intraoperatively.

In groups A and C, morphine was also injected in the epidural catheter at the first injection at a dose of 4–5 mg. In groups B and D, morphine was not injected into the epidural space.

The degree of effectiveness of postoperative analgesia was estimated by the consumption of bupivacaine and narcotic analgesics in the postoperative period, the subjective indicators of pain on the Pain Scale at rest and when coughing, the time of recovery of intestinal motility and the beginning of movement, as well as gas levels in arterial blood and the presence of complications including apnea when using morphine.

In groups C and D, the intensive therapy was carried out in the form of antioxidant therapy for two days before the operation, intraoperatively and three days in the postoperative period.

To measure the concentration of IgA and CD3+, blood samples were obtained before the operation and after 4 and 24 hours after the operation. The concentration of immunoglobulin class A was determined by the method of radial immunodiffusion in a gel containing monospecific anti-immunoglobulin serum according to Mancini. The determination of the subpopulation composition of the relative number of blood lymphocytes was based on the assessment of their surface phenotype in the form of the presence of a CD3+ Fc fragment, determined by flow cytometry using reagents on a flow cytometer "Partec CyFlow".

A study of the overall health-related quality of life was carried out using the standard validated Short Questionnaire for Health Status Assessment SF-36, using the evidence-based methodology (the quality of life is directly proportional to the number of points) in a shortened follow-up period of up to 1 week. Based on the results of the analysis of the answers to its questions, a socio-psychological profile of the patient [13] was formed, including the parameters: physical functioning (PF), role of physical functioning (RP), pain intensity (BR), general health (GH), vitality (VT), social functioning (SF), role

of emotional functioning (RF), mental health (MH). The parameters of the overall quality of life were assessed on a 100-point scale.

A preliminary evaluation of the distribution of the indicators was carried out by a visual method and using the Shapiro-Wilk criterion. The statistical processing of the results was carried out using the Statistica 10 software package, using the Wilcoxon-Mann-Whitney test. For each sample, the median (Me), the upper and lower quartiles [Q1; Q3] were determined. The statistical significance of differences in the indices of the experimental group from the comparison group was estimated according to the Mann-Whitney U test. The results obtained are given in the form of an arithmetic mean-square deviation. Differences were considered statistically significant at $p < 0.05$ or tended to be reliable at $0.1 > p > 0.05$.

Results

No one reported the absence or one-sidedness of the epidural block, which indicates that anesthesiologists are sufficiently qualified. According to pulse oximetry, the saturation (SpO_2) during surgery was within 96–100 %. A decrease in PO_2 and an increase in PCO_2 saturation was observed only when epidural morphine was used, and in two cases, naloxone was required.

We determined pain at rest and when coughing on subjective sensations on a ten-point scale, consumption of morphine and bupivacaine, motor block using the Bromage scale (1 = no motor block, 2 = just able to flex knees with free movement of feet, 3 = unable to flex knees, 4 = unable to move legs or feet), hemodynamic parameters (blood pressure, heart rate and central venous pressure). The ability to perform movements in bed was evaluated. Bowel repair was assessed by listening to intestinal motility. Side effects associated with opioid or epidural analgesia, such as nausea, vomiting, itching or respiratory depression, and the need for naloxone have been noted (Table 1).

To measure the concentration of IgA and CD3+, blood samples were obtained before the operation and 4 and 24 hours after the operation (Fig. 1, 2).

The Fig. 3 presents an evaluation of the health-related quality of life of patients during multiorgan resections in groups with and without antioxidant protection.

Discussion

According to the literature data, the effect of oxidative stress on all cells of the human body occurs through damage, and sometimes their destruction in the form of apoptosis as a programmed cell death or excessive exposure to active forms of oxygen can be the primary cell death.

In the postoperative period, indices of pain at rest and during coughing, hemodynamic parameters, time to return to bowel function and movement in bed, as well as gas levels in arterial blood were recorded. We studied the side effects associated with opioid or epidural analgesia,

Table 1. Evaluation of the degree of pain and comfort for the patient by the selected groups

Parameter	Group A	Group B	Group C	Group D
Pain score at rest	8–10	8–9	8–9	8–9
Pain score at cough	7–8	7–8	6–7	8
Morphine requirement, %	15.5 ± 2.1	25.0 ± 1.9	10.0 ± 3.4	35.0 ± 4.2
Motor block on Bromage scale	4	3	4	4
The presence of intestinal motility, %	75.4 ± 7.5	85.0 ± 11.2	87.0 ± 9.7	84.0 ± 7.8
Nausea, vomiting, itching	45.0 ± 4.5	3.0 ± 1.3	39.0 ± 5.7	2.0 ± 1.2
Respiratory depression	21.0 ± 2.3	5.0 ± 1.7	17.0 ± 3.2	4.0 ± 1.4
Naloxone requirement	2	–	–	–

Notes: data are presented as mean ± SD, or numbers (%), as appropriate. No significant differences were found between the groups.

the presence of respiratory depression, as well as the need for the introduction of naloxone.

Our studies showed that respiratory depression in cases of epidural morphine use was observed when administered the next morning after surgery. In particular, after the introduction of a narcotic anesthetic medication for the purpose of anesthesia in the morning, two patients stopped breathing, which required an auxiliary ventilator with a mask and the introduction of naloxone. At the same time, in the first case after 8 minutes, and in the second case after 11 minutes, the patients breathed independently and the PO₂ and PCO₂ indicators fully recovered. In the future, these patients did not cause any discomfort, and, moreover, they were unaware of their presence until they were told about it. It is possible, when following the recommendation not to inject narcotic painkillers for at least twenty-four hours after the administration of morphine into the epidural space, but to manage to administer bupivacaine into the epidural space and introduce non-narcotic analgesics, such apnea can be avoided.

Also, when using epidural morphine (which follows from the data in Fig. 1 and 2), a slight deterioration in immunity indices was revealed, although there was no statistically significant difference.

Preoperative levels of IgA and CD3+ are the same; their level reached a maximum after four hours, decreasing by 10–15 % in twenty-four hours after surgery in all groups. This indicates that in the group of L-ornithine L-aspartate with quercetin complex with povidone therapy, we had the best values of markers of systemic chronic inflammation.

The assessment of the health-related quality of life of patients during multiorgan resections revealed higher rates in group B, in which an antioxidant protection was carried out (Fig. 3). The Fig. 3 demonstrates the evaluation of the quality of life during multiorgan resections that is higher in group B except for role of physical functioning with the reliability of differences of the changes in the indices at p < 0.05.

The results suggest that in the group using epidural morphine, the degree of effectiveness of anesthesia was sufficient, but there were registered the complications,

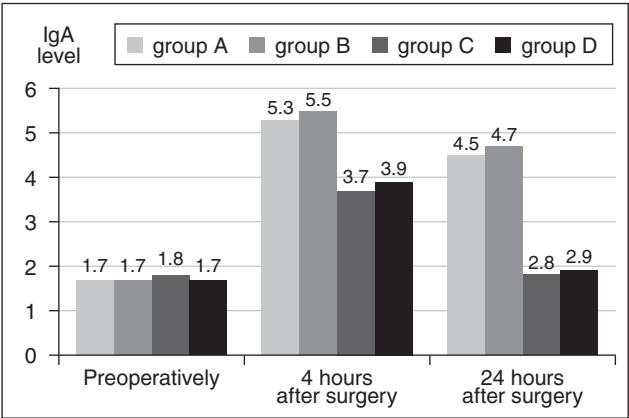


Figure 1. The average concentration of IgA (g/l) is relative in groups (p < 0.05)

Notes (here and in Fig. 2): group A — the patients undergoing combined general anesthesia with epidural morphine analgesia; group B — the patients undergoing combined general anesthesia with epidural analgesia without morphine; group C — the patients undergoing combined general anesthesia with epidural analgesia, who received antioxidant protection; group D — the patients undergoing combined general anesthesia with epidural analgesia without morphine, who received antioxidant protection.

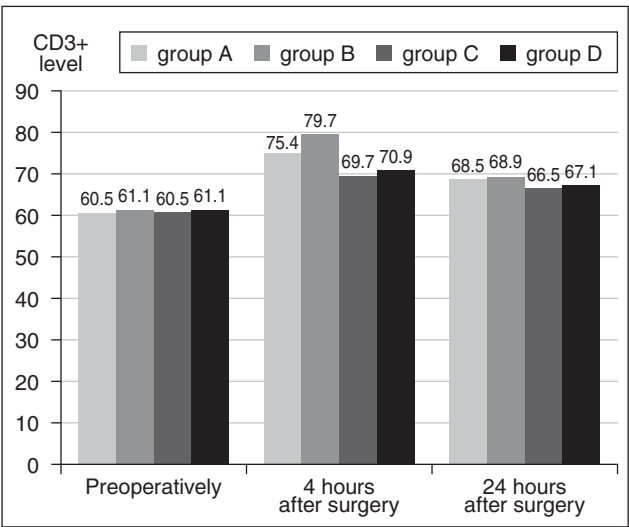


Figure 2. The average concentration of CD3+ (%) is relative in groups (p < 0.05)

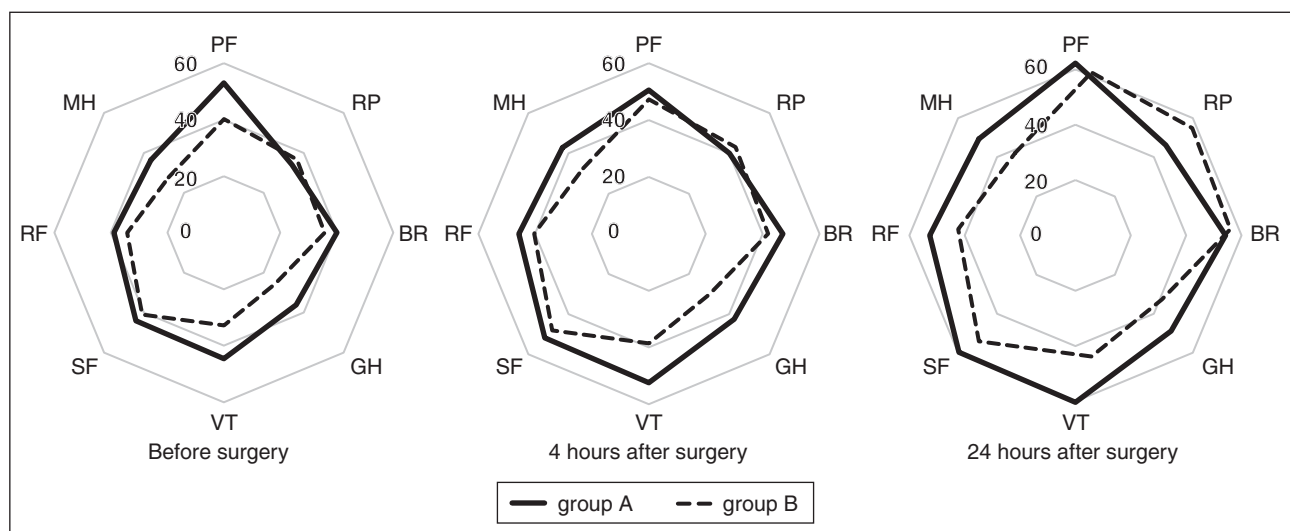


Figure 3. The structure of quality of life in cancer patients with multiorgan resections

Notes: group A — a group of patients, in which antioxidant agents had not been previously used; group B — a group of people, who received antioxidant protection. PF — physical functioning, RP — role of physical functioning, BR — intensity of pain, GH — general health, VT — vitality, SF — social functioning, RF — role of emotional functioning, MH — mental health.

including in the form of apnea while using morphine and a slight deterioration in immunity parameters. When applying the redox therapy, we have achieved improvement both in quality of life and more significant in immunity.

Conclusions

The results of our research demonstrated that respiratory depression in cases of epidural morphine use was observed when administering a narcotic analgesic drug the next morning after surgery. We do not exclude that when following the recommendation not to inject narcotic drugs for at least twenty-four hours after the administration of morphine into the epidural space, but to manage the administration of bupivacaine into the epidural space and introduce non-narcotic analgesics, such apnea can be avoided. Such studies, due to the low occurrence, require further evaluation.

The results indicate that in the group with redox therapy, we achieved improvement both in quality of life and overall survival rates and indicators of cellular and humoral immunity.

Thus, combined epidural anesthesia without morphine against the background of correction of redox metabolism in cancer patients with multiorgan resections is more comfortable for patients, less dangerous due to the lack of development of apnea, psychoemotional and economically justified, which indicates its priority using.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Information on each author contribution: M.V. Krasnoselskiy — concept and design of the study; Ye.M. Krutko — design of the study, collection of materials; E.S. Protchenko — collection and processing of the materials; Ye.V. Shulga — data analysis, collection of materials, text writing; M.V. Shulga — text writing.

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Порівняння ефективності комбінованої анестезії з використанням епідурального морфіну та без нього на тлі корекції окисно-відновного метаболізму в онкохворих з мультиорганими оперативними втручаннями

Резюме. Актуальність. На сьогодні недостатньо даних щодо післяопераційного епідурального знеболювання з використанням морфіну та проведення окисно-відновної терапії в онкохворих із мультиорганими оперативними втручаннями з подальшою оцінкою показників імунітету. **Мета роботи:** вивчення інтраопераційного використання епідурального морфіну порівняно з комбінованою загальною епідуральною анестезією, а також проведення окисно-відновної терапії в онкохворих із мультиорганими оперативними втручаннями з оцінкою показників імунітету для забезпечення анестезії з випереджаючою терапією можливих ускладнень та отримання більш комфортного стану пацієнтів. **Матеріали та методи.** Під час дослідження було обстежено 117 пацієнтів із місцево-поширеним пухлинним процесом шлунково-кишкового тракту з мультиорганими хірургічними втручаннями за життєвими показаннями (67,6 ± 3,7 року). Усі пацієнти були розподілені на чотири групи залежно від типу анестезії та антиоксидантної терапії. Були виділені групи з інтраопераційним використанням епідурального морфіну та без нього. Як антиоксидантну терапію використовували L-орнітин L-аспаратат з комплексом кверцетину з повідоном. Вимірювали показники клітинного та гуморального імуніте-

ту на прикладі субпопуляційного визначення відносної кількості лімфоцитів CD3+ та IgA до і через 4 і 24 години після операції. Загальну якість життя, пов'язану зі здоров'ям, оцінювали із застосуванням стандартного «Короткого опитувальника оцінки статусу здоров'я» SF-36 за науково обґрунтованою методологією. **Результати.** Отримані результати свідчать за те, що в групі з використанням епідурального морфіну ступінь ефективності знеболювання був достатнім, але були зареєстровані ускладнення, у тому числі у вигляді апное при використанні морфіну та незначного погіршення показників імунітету. При застосуванні окисно-відновної терапії ми досягли як поліпшення якості життя, так і більш значного покращання показників імунітету. **Висновки.** Таким чином, проведення комбінованої епідуральної анестезії без використання морфіну на тлі корекції окисно-відновного метаболізму в онкохворих із мультиорганими оперативними втручаннями більш комфортне для пацієнтів, менш небезпечне через відсутність розвитку апное, психоемоційно і економічно виправдане, що свідчить про її пріоритетне використання.

Ключові слова: епідуральний морфін; окисно-відновна терапія; мультиорганими оперативні втручання; комбінована загальна епідуральна анестезія

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Сравнение эффективности комбинированной анестезии с использованием эпидурального морфина и без него на фоне коррекции окислительно-восстановительного метаболизма у онкобольных с мультиорганными оперативными вмешательствами

Резюме. Актуальность. На сегодня недостаточно данных о послеоперационном эпидуральном обезболивании с использованием морфина и проведении окислительно-восстановительной терапии у онкобольных с мультиорганными оперативными вмешательствами с оценкой показателей иммунитета. **Цель работы:** изучение интраоперационного использования эпидурального морфина по сравнению с комбинированной общей эпидуральной анестезией, а также проведение окислительно-восстановительной терапии у онкобольных с мультиорганными оперативными вмешательствами с оценкой показателей иммунитета для обеспечения анестезии с опережающей терапией возможных осложнений и получения более комфортного состояния пациентов. **Материалы и методы.** В ходе работы было обследовано 117 пациентов с местно-распространенным опухолевым процессом желудочно-кишечного тракта с мультиорганными хирургическими вмешательствами по жизненным показаниям ($67,6 \pm 3,7$ года). Все пациенты были разделены на четыре группы в зависимости от типа анестезии и антиоксидантной терапии. Были выделены группы с интраоперационным использованием эпидурального морфина и без него. В качестве антиоксидантной терапии использовали L-орнитин L-аспартат с комплексом кверцетина с пивидомом. Измерялись показатели клеточного и гуморального иммунитета на примере субпопуляционного определе-

ния относительного количества лимфоцитов CD3+ и IgA до операции и через 4 и 24 часа после операции. Общее качество жизни, связанное со здоровьем, оценивали с применением стандартного «Краткого опросника оценки статуса здоровья» SF-36 по научно обоснованной методологии. **Результаты.** Полученные результаты свидетельствуют о том, что в группе с использованием эпидурального морфина степень эффективности обезбоживания была достаточной, но были зарегистрированы осложнения, в том числе в виде апноэ при использовании морфина и незначительное ухудшение показателей иммунитета. При применении окислительно-восстановительной терапии мы достигли как улучшения качества жизни, так и более значительного улучшения показателей иммунитета. **Выводы.** Таким образом, проведение комбинированной эпидуральной анестезии без использования морфина на фоне коррекции окислительно-восстановительного метаболизма у онкобольных с мультиорганными оперативными вмешательствами более комфортно для пациентов, менее опасно из-за отсутствия развития апноэ, психоэмоционально и экономически оправдано, что свидетельствует о ее приоритетном использовании.

Ключевые слова: эпидуральный морфин; окислительно-восстановительная терапия; мультиорганные оперативные вмешательства; комбинированная общая эпидуральная анестезия