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REGIONAL ANESTHESIA AND THE IMMUNE COMPONENT STRESS RESPONSE IN ONCOSURGERY

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✓ ***Resume***

In the current review the ability of regional anesthesia and analgesia to improve the results of surgical interventions in oncology due to the limiting effect on the immune and neuro – endocrine component of the stress response was examined. It was marked that the local anesthetics possessed the ability to reduce cell proliferation in cancers. The literature review was conducted, proving that regional anesthesia/analgesia considered as an essential component of anesthesia and the method of choice of postoperative analgesia in oncosurgery.

Key words: oncosurgery, stress response, immunity, anesthesia.

РЕГИОНАРНАЯ АНЕСТЕЗИЯ И ИММУННЫЙ КОМПОНЕНТ СТРЕССОВОЙ РЕАКЦИИ В ОНКОХИРУРГИИ

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✓ ***Резюме***

В обзоре рассмотрено влияние регионарной анестезии и анальгезии на иммунный компонент стресс-ответа как один из возможных путей улучшения результатов хирургических вмешательств в онкологии. Отмечена способность местных анестетиков, путем лимитирующего влияния на данный процесс, снижать пролиферацию раковых клеток. Проведен анализ литературы, доказывающий, что регионарные блокады являются наиболее оптимальным и необходимым компонентом анестезиологического обеспечения оперативных вмешательств в онкологии и методом выбора послеоперационной аналгезии у пациентов после онкологических операций с учетом их положительного влияния на иммунный компонент стресс-ответа.

Ключевые слова: онкохирургия, стресс-ответ, иммунитет, регионарная анестезия, влияние на иммунитет.

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✓ ***Rezyume***

Ushbu maqolada onkologiyada jarrohlik aralashuvlar natijalarini yaxshilashning mumkin bo'lgan usullaridan biri sifatida regionar behushlik va anageziyaning stress reaktsiyasining immun komponentiga ta'siri ko'rib chiqildi. Mahalliy anesteziklarning ushbu jarayonga ta'sirini cheklash orqali saraton hujayralarining ko'payishini kamaytirish qobiliyati qayd etildi. Adabiyotlar tahlili o'tkazildi, bu regionar blokadalar onkologiyada jarrohlik aralashuvlarni anestetik boshqarishning eng maqbul va zarur komponenti va onkologik operatsiyalardan so'nggi bemorlarda ularning ijobiy ta'sirini hisobga olgan holda stress reaksiyasining immun komponenti operatsiyadan keyingi analgeziya uchun tanlov usuli ekanligini isbotladi.

Kalit so'zlar: onkojarrohlik, stressga javob, immunitet, regional behushlik, immunitetga ta'siri.

Relevance

At present, there is no doubt about the exceptional importance of choosing the optimal method of anesthetic management in the perioperative period, which determines the effectiveness of surgical treatment in general. In this regard, the choice of anesthesia for surgical interventions in oncology is more important than anywhere else, due to their extensiveness, trauma and considerable duration. In addition, patients with malignant neoplasms are often elderly, have severe comorbidities, metabolic disorders, secondary immunodeficiencies caused by the action of the tumor. That is why it is very important to choose the most optimal and effective method of anesthesia, which would allow, first of all, to create adequate nociceptive protection with multiple points of influence on the conduction system of pain, would restrain the cascade of local inflammatory reactions to surgical trauma and provide minimal immunosuppression, as well as early activation and rehabilitation of the patient. In this review, we will focus on regional blockades in combination with general anesthesia, which best meet the above requirements for anesthetic management in oncosurgery.

The protective effect of regional anesthesia/analgesia is primarily due to the pharmacological properties of drugs used for this type of anesthesia, namely, their ability to reduce the release of endogenous opiates, reduce the production of biologically active substances that stimulate tumor growth and have a pro-inflammatory and immunosuppressive effect [7, 21, 29].

Local anesthetics (LA) used in regional anesthesia are known to play an important role in preventing surgical stress response. Their effect is due to a pronounced effect on various cells of the immune system. Thus, it was shown that low concentrations of MA prevent excessive activation of leukocytes, inhibit their adhesion to epithelial cells, and reduce the production of immunoactive pro-inflammatory substances such as histamine, leukotriene B4, and prostaglandin E2. These substances are mediators of inflammation and pain, play a leading role in the formation of tissue edema [32]. In experiments, it was found that the systemic use of MA significantly reduces both the pain syndrome and the production of pro-inflammatory substances. The mechanisms by which these drugs exert their action are not well understood; however, they suggest selective inhibition of the Gq protein, which activates phospholipase C and, as a result, is involved in inflammatory reactions [32]. It should also be noted that a series of studies also showed the organoprotective effect of LA on various models of damage to internal organs - acute myocardial infarction, acute lung injury, postischemic encephalopathy, inflammatory diseases of the gastrointestinal tract, etc. [31].

Thus, in vitro studies have shown that the local anesthetic lidocaine, widely used both in domestic and international anesthetic practice during regional blockades, has a direct inhibitory effect on epidermal growth factor receptors, thereby suppressing the proliferation of tumor cells and their invasive potential, reduces the ability of polymorphonuclear neutrophils for endothelial adhesion, migration, phagocytosis, and secretion of pro-inflammatory cytokines [28]. There are reports in the literature that systemic intravenous administration of lidocaine during abdominal operations also causes a significant decrease in pain syndrome and cytokine response, makes it possible to reduce opioid consumption, and also has the ability, along with epidural analgesia, to accelerate postoperative recovery of gastrointestinal motility [5].

Another representative of the MA group of amides, ropivacaine, inhibits both the growth of tumor cells [9] and their ability to metastasize [15]. Compared to bupivacaine and lidocaine, ropivacaine has more pronounced immunoregulatory properties - against the background of the most traumatic manipulations, a decrease in the production of pro-inflammatory intelukin 1 and an increase in the secretion of immunoregulatory interleukin 2 were observed. This, in turn, contributed to the normalization of most immunological parameters, primarily those characterizing T- cellular link of immunity [1, 13].

Another issue of interest from the point of view of the mechanisms of the stress-limiting effect of regional anesthesia is the analysis of the effectiveness of epidural and intrathecal administration of narcotic analgesics. The mechanism of their action is still not entirely clear. It is believed that with bolus administration, lipophilic narcotic analgesics act at the spinal level, while with prolonged epidural infusion, they act at the supraspinal level [28]. At the same time, under conditions of general anesthesia and in combination with epidural administration of a local anesthetic, segmental effects begin to predominate with the infusion method of administration. One way or another, epidurally administered narcotic analgesics act more selectively than local anesthetics (mainly at the level of the dorsal horns of the spinal cord), blocking only afferent stimulation [19]. On the one hand, this can be

considered as some advantage, since the absence of a sympathetic block during epidural anesthesia with narcotic analgesics almost completely excludes the development of arterial hypotension [14]. On the other hand, despite a good analgesic effect, regional analgesia with narcotic analgesics has a minimal effect on the endocrine-metabolic [31] and inflammatory response [14], which is explained by the absence of sympathetic blockade. However, the fact that the administration of narcotic analgesics intrathecally or epidurally allows to reduce the doses of narcotic drugs administered systemically and having a pronounced immunosuppressive effect remains undeniable. Immune disorders and the release of pro-inflammatory cytokines are also observed to a lesser extent with epidural anesthesia and analgesia compared with the systemic use of narcotic analgesics. A relationship has also been found between a high dose of opioids in the first 96 hours after surgery and cancer recurrence in the first 5 years [1, 8, 17]. At the same time, one cannot but note the ability of regional anesthesia to accelerate the postoperative recovery of gastrointestinal motility, which creates the prerequisites for the early start of enteral nutrition, and this, in turn, has a positive effect, among other things, on the immunological status of a cancer patient [32] .

An analysis of the literature allows us to conclude that various types of regional blockades using MA have a number of advantages over general anesthesia for surgical interventions in oncology [29]. Thus, prolonged epidural analgesia, along with an improvement in the quality of postoperative analgesia, makes it possible to achieve the most pronounced limiting effect on all the main components of the surgical stress response. It has been shown that neuraxial anesthesia/analgesia in gynecological and traumatic upper abdominal surgical interventions has a positive effect on laboratory parameters of stress response: it reduces the concentration of cortisol in the blood, excretion of catecholamines in the urine, and reduces the severity of lipid peroxidation processes [2, 10, 11]. At the same time, a more pronounced effect was noted with epidural anesthesia with lidocaine in comparison with systemic or epidural use of fentanyl [31].

Epidural anesthesia and analgesia have been shown to be effective in preventing protein and carbohydrate metabolism disorders, ensuring better absorption of energy substrates, and reducing the incidence of insulin resistance [9, 13, 24]. It should be noted that epidural anesthesia has the most pronounced effect on the endocrine and metabolic components of the surgical stress response during operations on the organs of the lower abdominal cavity. Classical works demonstrate that an extensive epidural block with local anesthetics effectively suppresses the neuroendocrine and metabolic response during operations on the lower floor of the abdominal cavity [25], while during operations on the upper floor, only the glycemic response is limited with minimal effect on the level of "stress" hormones [20].

According to the literature data, spinal anesthesia also has a distinct stress-limiting effect [5, 13], in which the creation of any significant concentration of MA in plasma seems unlikely. During operations on the organs of the lower abdominal cavity, prolonged spinal analgesia provides even more pronounced suppression of the surgical stress response compared to epidural [30]. The authors believe that this is due to the greater intensity ("density") of the regional blockade. In this regard, it can be assumed that the systemic action of MA is not the only and probably not the main mechanism of the stress-limiting effect of regional anesthesia/analgesia.

Paravertebral blockade deserves special attention, which has sufficient effectiveness both in thoracic and abdominal surgery and which is not inferior in analgesic effect to central neuraxial blocks. It represents a kind of compromise between neuraxial and peripheral nerve blockade. This blockade is comparable in efficiency to epidural anesthesia not only in terms of analgesic effect, but also in terms of the effect on the surgical stress response [12]. At the same time, the development is not accompanied by a hemodynamically significant sympathetic block with symptoms of hypotension. The explanation for this may be that with paravertebral anesthesia and analgesia, as well as with epidural, blockade is achieved not only of afferent, but also of efferent sympathetic impulses. Less severity of hemodynamic disturbances is considered as an additional advantage of the method [6]. This type of anesthesia in combination with general anesthesia is indicated in case of need for unilateral somatic and sympathetic blockade, for example, in such operations as mastectomy, nephrectomy, cholecystectomy, as well as in thoracic surgery.

The results of the influence of regional anesthesia on improving the long-term results of surgical interventions in oncology, judging by the literature data, are not so unambiguous. There are conflicting

data on the effect of neuraxial blocks on the incidence of recurrence and metastasis of malignant neoplasms.

The positive effect of regional anesthesia on the course of the oncological process has been demonstrated in a number of studies. Thus, it is shown that it is intraoperative epidural anesthesia (in contrast to postoperative analgesia) that prevents immune dysfunction and reduces the risk of metastasis of malignant neoplasms. From the point of view of the pathophysiology of the surgical stress response, this seems quite logical, since it is during the operation that tissue damage occurs and the surgical stress response is triggered. As one of the possible mechanisms for limiting inflammatory and immunological changes under the influence of regional anesthesia, a decrease in intraoperative doses of inhalation anesthetics and narcotic analgesics with an immunosuppressive effect is considered [16]. Obviously, postoperative analgesia has nothing to do with this. The presence of a distinct stress-limiting effect of spinal anesthesia, which is much longer than the duration of the anesthesia itself, also testifies in favor of the greater importance of intraoperative regional anesthesia compared to postoperative analgesia [5, 31].

Retrospective studies with a follow-up period of 2.8 to 12.8 years have been published showing a 57% reduction in the recurrence rate of prostate cancer in patients who underwent epidural anesthesia compared with the use of systemic opioids [18].

It was also shown that in patients suffering from breast cancer, the use of general anesthesia in combination with paravertebral blockade with prolongation in the postoperative period revealed a 4-fold decrease in the frequency of recurrence of the disease, compared with patients who used general anesthesia with morphine [27]. Another study demonstrated a change in the cytokine status and a decrease in the concentration of MMP-3 and MMP-9 metalloproteinases in the blood of patients operated on for breast cancer under general anesthesia with propofol in combination with paravertebral blockade. This phenomenon of a decrease in the level of these proteins against the background of a combination of general anesthesia with paravertebral blockade plays a positive role, since these proteins are considered important regulators of neoplastic processes that affect the differentiation, proliferation and survival of tumor cells, as well as the processes of its microvascularization. In addition, a decrease in the concentration of both pro- (IL-1β) and anti-inflammatory cytokines (IL-10) in blood plasma was established. It should be noted that the function of T-cytotoxic cells studied in this work was also more pronounced in the group of patients in whom general anesthesia was combined with unilateral paravertebral blockade [23].

It has been established that both general anesthesia with sevoflurane and surgery itself suppress the antitumor function of CD4+ T-helpers, and the combined use of spinal anesthesia reduces the immunosuppressive effect [29]. In the same study, a significantly lower incidence of liver metastases was noted in the group of patients who underwent general anesthesia with sevoflurane in combination with spinal anesthesia compared with the "pure" sevoflurane group.

Sachidanand Jee Bharati, Tumul Chowdhury in 2016 also demonstrated the negative impact of surgical stress and general anesthesia on the immune system, which contributed to tumor progression and the development of metastases [22].

A number of works have been published, the authors of which show the effect of local and regional anesthesia on reducing the risk and frequency of cancer recurrence. Thus, a retrospective study including 655 patients from two Swedish clinics revealed a significant decrease in mortality within 1–5 years after surgery for rectal cancer and who received prolonged EA in the early postoperative period, compared with those who underwent patient-controlled analgesia with morphine. (25% and 34% respectively) [30].

A meta-analysis conducted in 2015 in the Netherlands included all studies published to date regarding the use of epidural anesthesia and patient survival after surgery for colon cancer. The sample consisted of more than 43 thousand patients over 25 years (from January 1990 to June 2014). As a result, 1 prospective and 4 retrospective studies have shown better survival up to 5 years with epidural anesthesia. After 5 years, 62% survived with epidural anesthesia, and 54% of operated patients without epidural anesthesia. None of the studies showed at least a negative effect of regional anesthesia on patient survival [8].

However, there are a number of studies where no relationship was found between the survival of patients after oncosurgical interventions and the type of anesthesia performed by them. So, in a study conducted in the Department of Anesthesiology of the Oncology Center of Zhejiang Province (China), 273 patients took part, while general anesthesia was performed in 116 patients, and 157 - epidural. An analysis of the results using the Cox regression model showed that there were no significant differences in survival rates between the two groups of patients operated on under different types of anesthesia [23].

A retrospective study conducted at Chunnam University Hospital analyzed 161 case histories of patients who underwent transurethral resection of a bladder tumor. Of these, 24 patients were operated on under general anesthesia, and 137 under regional anesthesia. No statistically significant differences were found (using logistic regression analysis and χ-square test) in 5-year survival of patients [22].

In one of the works, the influence of the types of anesthesia performed in patients with oncopathology on the outcome and recurrence rate of the disease was analyzed. Very conflicting results have been obtained. For example, no relationship has been found between epidural anesthesia and disease outcome in patients with colorectal cancer and prostate cancer [21].

In a study by Abraham M. Tsigonis et al. it was shown that such indicators as overall survival, event-free survival and local recurrence did not depend on the choice of the method of anesthesia in patients with stage 0–III breast cancer [27].

A retrospective analysis performed in a recently published study showed that epidural anesthesia in patients with kidney cancer who underwent kidney resection or radical nephrectomy did not significantly improve the survival rate associated with the main diagnosis. At the same time, the use of epidural anesthesia increased the overall survival of patients [26].

Conclusion

Thus, the literature data allow us to conclude that the development of surgical stress response during highly traumatic operations in oncology is directly related to clinically significant homeostasis disorders that require correction, as well as to the occurrence of serious complications associated with changes in the neuroendocrine status and metabolism, which negatively affects the immunological status of a cancer patient and negatively affects the oncoprocess.

Despite the existence of many approaches to the correction of individual parts of the surgical stress response, one of the most promising and real possibilities for its complex limitation is the use of anesthesia and analgesia techniques, which make it possible to reduce intraoperative doses of inhalation anesthetics and narcotic analgesics with immunosuppressive properties.

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