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THE INFLUENCE OF THE CHOICE OF ANESTHESIA METHOD ON THE IMMUNE RESPONSE OF PATIENTS WHO UNDERWENT RADICAL SURGERY FOR BREAST CANCER

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✓ ***Resume***

The aim of this study was to determine the impact of anesthesia techniques on selected parameters of patient immunity considering the evidence of relationship between the anesthesia methods and immune status and, consequently, the incidence of cancer recurrence. The patients who underwent breast cancer surgery under TIVA had lower blood leukocyte counts and levels of MMP-9, which is involved in the remodeling of extracellular matrix, compared with thos operated on under IA, suggesting that the anesthesia method may have an impact on the immunity of breast cancer patients

Keywords: anesthesia; breast cancer; surgery; immunomodulation; inhaled anesthesia; intravenous anesthesia

ВЛИЯНИЕ ВЫБОРА МЕТОДА АНЕСТЕЗИИ НА ИММУННЫЙ ОТВЕТ ПАЦИЕНТОК ПЕРЕНЕСШИХ РАДИКАЛЬНУЮ ОПЕРАЦИЮ ПО ПОВОДУ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

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✓ ***Резюме***

Целью данного исследования было определить влияние методов анестезии на отдельные параметры иммунитета пациента, учитывая очевидную взаимосвязь между методами анестезии и иммунным статусом и, следовательно, частотой рецидивов рака. У пациенток, перенесших операцию по удалению рака молочной железы в рамках TIVA, было более низкое количество лейкоцитов в крови и уровень MMP-9, который участвует в ремоделировании внеклеточного матрикса, по сравнению с пациентками, оперированными в рамках IA, что позволяет предположить, что метод анестезии может оказывать влияние на иммунитет больных раком молочной железы.

Ключевые слова: анестезия; рак молочной железы; хирургия; иммуномодуляция; ингаляционная анестезия; внутривенная анестезия

ANESTEZIYA USULINI TANLASHNING KO'KRAK BEZI SARATONI UCHUN RADIKAL OPERATSIYA QILINGAN BEMORLARNING IMMUNITETIGA TA'SIRI

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✓ ***Resume***

Ushbu tadqiqot maqsadi, binobarin, saraton takrorlanish chastotasi behushlik usullari va immun holati va o'rtasidagi munosabatlar dalil inobatga sabr immunitet tanlangan parametrlari haqida narkoz metodlarni ta'sirini aniqlash uchun edi. Tiva ostida ko'krak bezi saratoni operatsiya qilindi bemorlar behushlik usuli ta'sir ko'rsatishi mumkin, deb ishora, thos IA ostida operatsiya bilan solishtirganda, kam qon leykotsitlar soni va hujayra tashqari matritsasi ta'mirlanishi ishtirok MMP-9, darajasini edi ko'krak saratoni bemorlarning immunitet

Kalit so'zlar: behushlik; ko'krak saratoni; jarrohlik; immunomodulyatsiya; inhaler behushlik; vena ichiga behushlik

Relevance

Modern oncology assumes a multidisciplinary approach to the choice of treatment method: depending on the type of tumor and individual characteristics of the patient, chemo- and (or) radiation therapy, immunomodulatory drugs and (or) elements of genetic engineering, as well as biologically active substances that modulate the cell cycle (for example, inhibitors of immune response control points) can be used [1, 2]. Radical surgery is still the most effective and most widely used method of treating solid tumors: it is indicated in at least 80% of newly diagnosed cancer patients [3]. And the trend of recent years indicates a high probability of growth of the discussed indicator, at least in the foreseeable future [3]. For example, the need for surgical treatment of breast cancer (BC) in the world will increase from 3,022,883 operations in 2015 to 3,810,168 operations in 2030 [3].

Most surgical interventions for malignant tumors have been performed and are being performed under general anesthesia, and most research in the field of intraoperative protection has been limited to studying the features of anesthesia in various types of surgical interventions. However, new data are emerging today indicating that the use of inhalation anesthesia (IA) may be associated with a large number of adverse outcomes in the long term after radical operations, which, in turn, is explained by an allegedly higher incidence of tumor recurrence [4]. Halogen-containing anesthetics are considered responsible for the initiation of the described process, which are credited with influencing apoptosis, systemic inflammatory response and immunosuppression [5-8]. Thus, immunity seems to be the main link in the realization of the possible negative effect of anesthesia on postoperative survival rates in cancer patients. This coherent hypothesis, however, has not yet been sufficiently confirmed by the results of studies that could be considered convincing in the framework of evidence-based medicine [9]. Perhaps one of the significant drawbacks of previous meta-analyses was an attempt to combine too heterogeneous groups of patients in one study (different stages of cancer; significant differences in the volume and area of the operation and, of course, different levels of basic mortality).

In this regard, the purpose of this systematic review was to determine the impact of the choice of anesthesia method (TVA vs. II) on the serum concentration of proinflammatory cytokines and matrix metalloproteinases in patients operated for breast cancer.

Materials and methods

This meta-analysis complies with the recommendations of the "Guidelines on Preferred Reporting Elements for Systematic Reviews and Meta-analyses" (PRISMA) [10-13] and is registered in the PROSPERO system (CRD42021255272).

Research search and selection strategy. Two independent researchers (MYA and KK) searched for articles published over the past 10 years in the PubMed, Cochrane and Google Scholar databases. The meta-analysis included randomized controlled trials published in peer-reviewed journals, prospective and retrospective cohort studies comparing the effects of IA and TVA on the immunity of breast cancer patients. Experimental animal studies and studies with insufficient information to perform meta-analysis were excluded (for example, the absence of absolute values of quantitative parameters). After removing the duplicates, two reviewers selected publications suitable for analyzing the full-text version to resolve the issue of inclusion/non-inclusion in accordance with predetermined criteria. The final decision was made by consensus, and in case of discrepancies — by the Main Researcher. The search was performed in the form of queries for the following keywords: [anesthesia breast cancer / total intravenous anesthesia versus volatile anesthesia breast cancer / TIVA inhalation anesthesia breast cancer / breast cancer propofol / neutrophil-lymphocyte ratio breast cancer anesthesia / anesthesia immune cell / anesthesia immune response]. Additionally, the consideration of literary sources in the analyzed articles was used.

The flowchart of the selection of articles is presented in Fig. 1. Of the 1861 publications initially identified in databases, only five randomized and three non-randomized trials met the inclusion/exclusion criteria (637 patients: 320 in the TBA group and 317 in the IA group) and were analyzed.

Data collection. The following data were extracted from each study: design, anesthesia method, quantitative parameters of immune markers (determined by the authors of each initial study).

Статистический анализ. Данные проанализированы с использованием программного обеспечения «RevMan, версия 5.3, Северный Кокрейновский центр, Кокрейновское сотрудничество».

For the case when the authors presented the data in the form of a median (interquartile range) or average (confidence interval), the recommended conversion methods were used in the form of "average value ± standard deviation" [14, 15]. The heterogeneity of the studies was assessed using the heterogeneity coefficient I 2 and the Cochrane coefficient Q. Non-fish data were compared using the standardized mean difference (SMD) and its 95% confidence interval (CI). Two models were used to generalize the magnitude of the standardized difference in the mean values: a fixed model and a random effects model [16]. The random effects model was used in the case of moderate and high heterogeneity (defined as I2 > 60%).

The primary endpoint of the study was the neutrophil-lymphocytic index NLI on the first day of the postoperative period.

The secondary endpoints were leukocyte levels, IL-6, IL-10, MMP-3, MMP-9 at the specified time.

Assessment of the risk of systematic error. To assess the risk of systematic error, appropriate Cochrane tools were used for randomized (RoB 2) [17] and non-randomized studies (ROBINS-I) [18]. The articles included in the meta-analysis were independently assessed for the risk of systematic error by two reviewers (CC and MJ) and reviewed by a third (LB). Two statistical tests were used to assess the risk of systematic publication error: the Egger test [19] and the Run test (MedCalc Statistical Software, version 19.5.6) [20]. Funnel-shaped graphs (funnel-plot) were used to visually assess the systematic error of publication [21].

Results and discussions

Characteristics of the study. The characteristics of the studies included in this work are presented in the table.

Data analysis. No statistically significant intergroup differences were found with respect to the primary endpoint: the average value of NLI in the TWA group was 2.45±1.32 versus 2.74±1.72 in the IA group (SMD=-0.25; 95% CI: –0.65–0.17; p=0.240, I2=71%; three studies were included).

In Fig. 2, b presented a forest-plot of 4 studies that compared the content of leukocytes in the postoperative period in patients in the TVA and IA groups. Patients in the TVA group had a statistically significantly lower leukocyte count compared with patients who received inhaled anaesthetics (the average number of leukocytes in the TVA group=8.08±2.16×103/ml versus 8.75±2.26×103/ml in the IA group, SMD=-0.32; 95% CI: –0.58– -0.06; p=0.020; I2=58%). Visual inspection of the funnel-shaped graph, as well as Egger (p=0.005) and Bega (p=0.042) tests indicate the presence of a publication bias.

Two studies evaluated postoperative concentrations of matrix metalloproteinase-9. Patients receiving total intravenous anesthesia had a statistically significantly lower concentration of MMP-9 in the postoperative period compared with patients of the IA group (the average value of MMP-9 in the TBA group=204.7±86.6 ng/ml versus 237.0±84.8 ng/ml in the IA group; SMD=-0.35; 95% CI: –0.67–0.03; p=0.030; I2=0%).

There were no statistically significant differences in serum concentrations of cytokines and MMP-3:

- IL-6 (the average value of IL-6 in the TWA group was 215.8±170.5 pg/ml versus 232.8±148.4 pg/ml in the IA group; SMD=-0.34; 95% CI: – 0.82–0.33; p=0.404; I2=77%; four studies included),
- IL-10 (the average value of IL-10 in the TWA group is 789.9±714.7 pg/ml versus 723.4±470.0 pg/ml
- in the IA group; SMD=0.16; 95% CI: – 0.08–0.40; p=0.190;
- I2=10%; three studies were included) and
- MP3 (the average value of MMP-3 in the TWA group=341.4±697.1 ng/ml versus 507.3±1120.4 ng/ml
- in the IA group; SMD=-0.10; 95% CI: –0.99–0.80; p=0.830; I2=80%; two studies were included).

In general, two randomized controlled trials had a low risk of systematic error, while all observational studies were characterized by a critical risk of such an error.

In the course of this study, it was not possible to detect differences in the levels of NLI in the postoperative period in the compared groups. Given the high risk of systematic error in the initial observational studies, the absence of a statistical difference in the primary endpoint can be interpreted as a dubious result — we are unable to confirm or deny the effect of inhalation anesthesia on the immune status of patients who underwent radical surgery for breast cancer. This situation is very similar to the situation around the study of the effect of inhalation anesthesia on the immune status and mortality in cancer patients, in general: some researchers confirm this effect [30, 31], while others do not find it [9, 32]. And the results of the meta-analysis do not provide a definitive answer [33, 34]. It may be worth waiting for the results of the major research that is currently underway (NCT01975064, NCT04316013) and is even close to completion.

The detected intergroup difference in the number of leukocytes is unlikely to be interpreted in favor of one or another method of anesthesia, since this indicator in both the TWA and IA groups practically does not exceed the reference values. This observation only confirms the hypothesis expressed in the previous paragraph.

At the same time, patients with breast cancer who underwent surgery under IA conditions had higher postoperative MMP-9. In an experimental study by Leifler et al. [35] It has been shown that MMP-9 participates in the regulation of the antitumor innate immune response, thus influencing the metastatic activity of malignant neoplasms. The undoubted importance of the expression level of MMP-9 as a prognostic marker of survival in breast cancer was also confirmed in a large meta-analysis involving 15 studies (from 2001 to 2012) with 2,344 participants. The cited meta-analysis showed that positive expression of MMP-9 is associated with lower overall survival (adjusted hazard ratio, HR: 1.70, 95% CI: 1.41–2.04) and disease–free survival (adjusted HR: 1.54, 95% CI: 1.17-2.01) in patients with breast cancer [36]. Later, Ren et al. A meta-analysis of 28 studies involving 4,944 patients (including 9 studies of MMP-9, N=1044) was performed, confirming the negative effect of increased expression of MMP-9 on overall survival (relative risk (HR)=1,694. 95% CI: 1,347–2,129, $p<0.001$; HR=1,611. 95% CI: 1,419–1,830, $p<0.001$) [37].

Thus, the differences in MMP-9 levels observed in the present study in the compared groups do not allow us to discount the possible effect of IA on the immune status of patients with breast cancer and confirm the weak knowledge of the problem under discussion.

We did not record the effect of the compared anesthesia methods at the level of IL-6, IL-10 and MP3, which may indicate against the hypothesis of a negative effect of IA on the systemic inflammatory response and immunity in general.

Thus, contradictory data have been obtained that make it difficult to unambiguously assess the effect of the anesthesia method on the immune status of patients in the postoperative period after radical surgery for breast cancer.

Limitations. Significant statistical heterogeneity was found when combining the results of IL-6 and ILI assessment in a meta-analysis of various studies, which could affect the significance of the results obtained.

Only 3 out of 8 studies included in the meta-analysis had a "low" or "moderate" risk of systematic error, which limits the clinical significance of the results and dictates the need for a multicenter RCT to assess the effect of anesthesia on the immune parameters of patients with breast cancer.

In addition, the results were obtained from single-center hands, which are known to be able to overestimate the size of the intervention effect compared with multicenter RCTs [38, 39].

Nevertheless, today it is necessary to conduct a large multicenter RCT, in which the effect of IA on the development of the inflammatory process and the immune system in patients operated on for breast cancer will be comprehensively assessed in order to unambiguously answer the question whether the choice of anesthesia method affects the immune status of patients who underwent breast cancer surgery. Only a study devoted to the assessment of complications of the early postoperative period and long-term survival will allow us to recommend the use of IA or refrain from using this method of anesthesia in this type of surgery.

Conclusion

Patients with breast cancer operated on in the conditions of TVA had lower levels of MMP-9 compared to patients operated on in the conditions of IA, which does not exclude the possibility of a negative effect of IA on the immune status of patients with breast cancer. It is necessary to continue research on the effect of various types of anesthesia on the immune status of patients, possibly to study classical indicators of immune status: immunoglobulins, complement components, acute phase proteins (in particular, the determination of C-reactive protein by a highly sensitive method), indicators of cellular immunity.

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