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Review

THE EFFECT OF REGIONAL VS. GENERAL ANESTHESIA ON THE IMMUNE RESPONSE IN BREAST CANCER SURGERY: A NARRATIVE REVIEW OF THE LITERATURE

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ABSTRACT – For breast cancer patients, surgery remains the cornerstone in treatment. Perioperative and postoperative period is associated with impaired immune function that can have profound implications for cancer patients in terms of tumor recurrence and metastases. The three main factors include surgery and related neuroendocrine stress response, anesthetic drugs, including opioid analgesics and postoperative pain. The most investigated immune cells are natural killer (NK) cells that are affected by both anesthesia and surgery. It has been demonstrated that ketamine, thiopental, volatile anesthetics, fentanyl and morphine, but not propofol, remifentanil or tramadol reduce the number of circulating NK cells and depress their toxicity. The level of NK cells' cytotoxicity is inversely proportional to the stage and spread of cancer. Regional anesthesia and its potential beneficial effects on the perioperative immune response and long-term outcome after surgery has been investigated as an alternative to general anesthesia in patients undergoing breast cancer surgery. In this paper, we present a review of literature aimed to assess the impact of regional anesthesia techniques on the immune response in patients undergoing breast cancer surgery and how it compares to general anesthesia.

Keywords: *breast cancer surgery, general anesthesia, regional anesthesia, immunosuppression, immune response*

Introduction

Female breast cancer ranks as the most commonly diagnosed cancer, surpassing lung cancer and being the fifth cause of death due to cancer.[1] Most patients with breast cancer undergo surgery, either as a sole therapy or as part of treatment protocol. Traditionally, breast surgery has been performed under general anesthesia with the use of opioids in the perioperative and postoperative period. However, regional anesthesia techniques have been successfully used in combination with general anesthesia and are emerging as promising single techniques.[2] Regional techniques include thoracic epidural block, thoracic paravertebral block (PVB), intercostal nerve blocks and pectoral nerve blocks (PECS).[3] Among these, PECS blocks represent a recent and less invasive technique providing good analgesia with less complications.[4]

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It has been long known that the perioperative and postoperative period is associated with impaired immune function. The three main factors include surgery, related neuroendocrine stress responses and anesthetic drugs, including opioid analgesics and postoperative pain.[5,6,7] Surgical trauma is associated with stress response that may impact immune response and promote proliferation of cancer cells.[8] The most investigated immune cells are natural killer (NK) cells that are a type of cytotoxic lymphocytes that respond to virus-infected cells and other intracellular pathogens as well as tumor formation, inducing lysis without prior activation. They are a critical part of innate immunity, acting as the main defense against the intravascular spread of cancer.[9,10] Reduced NK cells' cytotoxicity (NKCC) is associated with poor cancer prognosis in breast cancer.[11] The level of NKCC is inversely proportional with the stage and metastases of cancer, especially in patients with breast cancer.[11]

Regional anesthetic techniques have been associated with modulatory effects on the inflammatory and immune response.[12,13,14] The aim of this study was to conduct a review of the literature to assess the impact of regional anesthesia techniques on the immune response in the patients undergoing breast cancer surgery and how it compares to general anesthesia.

The literature in this review was obtained from a search of the PUBMED database up until April 1, 2022. Results were restricted to English language. Search terms included *immune response and breast cancer surgery*, *immune response and anesthesia*, *anesthesia and natural killer cells*, *i.v. anesthetic drugs and immune response*, *volatile anesthetics and immune response*, *opioids and immune response*, *regional anesthesia and immune response*. Relevant references from articles identified in the references review were also obtained, and all primary sources were retrieved.

Surgery and the immune system

Surgical procedures cause stress and, therefore, a variety of immunological disturbances that result in immunosuppression during the postoperative period.[15] Immunosuppression is associated with impaired wound healing, increased incidence of cancer recurrence and reduced survival in cancer patients.[15] It is known now that surgery and a decrease in T lymphocyte numbers cause a shift in the balance between the immune-suppressive regulatory T lymphocytes and the immune promoting helper T and cytotoxic T cells in a predominance of T regulatory cells.[16] In addition to causing a decrease in the number of T lymphocytes, it also causes suppression of NK cells[17] and an increase in the number of neutrophils.[18] Authors have described that surgery results in inhibition of the phagocytic function of neutrophiles[19] and reduction of neutrophil motility.[20] Breast cancer surgery is necessary to cure breast cancer patients.[21] Surgical treatment varies from more invasive treatments such as mastectomy with dissection of axillary lymph nodes to less invasive ones, such as quadrantectomy and sentinel lymph node biopsy, which has recently been used more frequently due to progress in oncology treatments (neoadjuvant chemotherapy and radiotherapy). Boomsma et al. studied immunomodulation that was demonstrated in breast cancer surgery and the result was an increment of CRP, increase in the number of leukocytes and decrease in NK cells' activity.[21] Surgical trauma also causes an increase in cytokines as well as in plasma stress hormones that induce transient suppression of cell-mediated immunity.[22]

Anesthetic drugs and the immune system

Anesthetic drugs have also been associated with suppressing immune response. It has been proposed that they directly affect the function of NK cells, cytotoxic T cells, mononuclear cells and dendritic cells.[24,25]

I.V. anesthetics

Ketamine and thiopental, but not propofol, have been shown to reduce the number of circulating NK cells and depress their toxicity in rats.[26] A randomized prospective study comparing NKCC and interleukin-2 (IL-2) levels of patients receiving either propofol-remifentanil anesthesia with postoperative non-opioid analgesia (ketorolac) or sevoflurane-remifentanil anesthesia with postoperative fentanyl analgesia was performed on 48 patients. It was reported that the NKCC was increased in the propofol group, whereas there was a decrease in the sevoflurane-fentanyl group. There was no significant change in IL-2 in either group as well as no changes in total leukocyte, neutrophil and lymphocyte counts between the groups.[27] It has been shown that propofol has cyclooxygenase-2 inhibiting activity, reducing the production of prostaglandin E2, a mediator of pain and inflammation that inhibits NKCC.[28] Propofol is known to interfere with β-adrenergic signal transduction in adipocytes.[29] β-adrenergic stimulation may par-

tially explain its favorable impact on NK cells during the stress conditions.[30]

Volatile anesthetics

The effect of volatile anesthetics on immunity has been well documented and it has been reported that cell-mediated immunity is suppressed to a greater extent than the humoral immune response.[31,32,33] In an experimental study in mice using a 3% concentration of sevoflurane during a 40-minute single application per week for 3 weeks caused a significant decrease in peripheral lymphocyte and leukocyte counts.[33]

Markovic et al. demonstrated that halothane and isoflurane inhibit interferon-induced stimulation of NKCC of murine splenic mononuclear cells in vivo and in vitro.[34] Volatile anesthetics have the dose and time-dependent suppressive effects on NK cells and T lymphocytes.[35,36] Dagan and Segal reported that 2% to 6% sevoflurane caused peripheral lymphocyte apoptosis that was dose and time dependent.[35]

Pirbudak Cocelli et al. performed a randomized prospective study comparing the effects of sevoflurane and desflurane on neutrophil and T-cell populations. In both groups, a significant decrease in lymphocyte count was observed at 2 hours after induction. In the desflurane group, a significant decrease in the percentage of CD4 cells and CD4/CD8 ratio, a widely used measure of immunosuppression, and a significant increase in the neutrophil count and percentage of CD8 cells was observed. In the sevoflurane group a significant decrease in the percentage of NK cells was observed. At 24 hours after induction, a significant increase in the leukocyte and neutrophil counts was observed in both groups.[36]

Opioids

Both pain and opioid analgesics are known to cause immunosuppression.[37,5] Opioids have been shown to suppress both cell-mediated and humoral immunity.[38] This includes NK cells and phagocytic activity and production of immune-stimulating cytokines and antibodies.[39] Morphine induces immunosuppression that is mediated through binding to μ-opioid receptors on immune cells, particularly μ3-receptor which is morphine-sensitive and is responsible for its effect on the immunity.[40,41,42] Fentanyl is shown to have a suppressive effect on NK activity in rodent nonsurgical individuals, but it had positive effects in operative subjects.[43] In a study performed on seven healthy individuals who underwent no other procedure than the intravenous administration of fentanyl, it was demonstrated that a short-term in vivo exposure to fentanyl increases NKCC directed against a tumor cell target. This effect seemed to be caused by an increase in the number, but not the activity of NK cells in peripheral blood.[44] In contrast to these findings, a randomized study performed on 40 patients receiving either large or small dose fentanyl found a significant decrease in NKCC that was observed in both groups at 24 hours with the effect lasting longer in the large dose fentanyl group.[45] Remifentanil does not impair NK activity[46] and tramadol, which has noradrenergic and serotonergic activity in addition to its action at opioid receptors, stimulates NK cells activity.[47]

Regional anesthesia techniques and immune system

In a rat model of breast cancer metastasis, it has been shown that the NK cells function is better preserved and metastatic load to the lungs reduced by neuraxial anesthesia.[48,49] Buckley et al. performed a pilot study on 10 patients undergoing breast cancer surgery, comparing cytotoxicity of NK cells from the serum of patients who received a sevoflurane-opioid based anesthesia to the equal number of those who received propofol-PVB based anesthesia. The serum from propofol-PVB group led to a greater NKCC in vitro compared with serum from patients who received sevoflurane-opioid anesthesia.[13] In a follow-up of a study performed in patients undergoing breast cancer surgery, comparing propofol-PVB technique to a balanced general anesthesia with opioid analgesia, propofol-PVB induced increased levels of NK and T helper cell infiltration into breast cancer tissue compared to general anesthesia, but not of T suppressor cells or macrophages.[14] In a randomized study investigating the effect of PECS II block under general anesthesia on the immune function of breast cancer patients, a higher proportion of NK cells and improved killing activity as well as increased postoperative concentration of IL-2 has been found compared to general anesthesia without PECS block group.[12]

Discussion

Surgery remains the cornerstone in treatment of breast cancer. However, perioperative and postoperative periods are associated with brief, but significant immunosuppression which can have profound

implications for cancer patients in terms of tumor recurrence and metastasis.[15] Most anesthetic drugs have to date been investigated for their effect on immunity. Volatile anesthetics as well as i.v. agents such as ketamine and thiopental and opioid analgesics such as morphine and fentanyl have long been known to have detrimental effect on the immune response.[26,27,31,32,33,34,35,36, 38,39,45] On the other hand, propofol, remifentanil and tramadol do not appear to show this behavior.[26,28,46,47] Regional anesthesia and its potential beneficial effects on the perioperative immune response and long-term outcome after surgery have been investigated as an alternative to general anesthesia in patients undergoing breast cancer surgery.[12,13,14,48,49] The potential ability of regional anesthesia to improve long-term outcome is due to several different mechanisms that include attenuation of the immunosuppressive effect of the surgery by inhibiting the neuroendocrine stress response[51], by reducing the requirement of opioids in the postoperative period[52] and reducing the overall requirement for anesthetic drugs when regional anesthesia is used in addition to general anesthesia.[53] However, to date, there are very few prospective human studies investigating the effect of regional anesthesia on improving immune response in patients undergoing breast cancer surgery and to our knowledge, there are no published prospective human trials designed specifically to look at the effect of regional anesthesia as a single technique. In our opinion, there is great potential and need for further randomized prospective studies that include those performed on patients receiving regional anesthesia as a single technique, specifically PECS and modified PECS blocks and also investigating a wider array of inflammatory parameters.

Conclusion

Perioperative immunosuppression is a significant complication for breast cancer patients. Anesthetic technique and the choice of anesthetic drugs have an effect on immune system and may affect long-term outcome. Regional anesthesia appears to have beneficial effects on the perioperative immune response, however studies investigating this effect are scarce and none include regional anesthesia as a single technique, creating the need for a randomized prospective human trial to further investigate the role of regional technique in understanding the effect of anesthesia on immune response and long-term survival.

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Sažetak

UČINAK REGIONALNE VS. OPĆE ANESTEZIJE NA IMUNI ODGOVOR U KIRURGIJI KARCINOMA DOJKE; PREGLED LITERATURE

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Za pacijente s rakom dojke operacija je neizostavni dio terapijskog postupka. Predoperativno i postoperativno razdoblje je povezano s oslabljenom imunološkom funkcijom koja može imati značajne posljedice za bolesnike s karcinomom u smislu recidiva tumora i metastaza. Tri su glavna čimbenika odgovorna za takve promjene i uključuju operaciju i s njom povezan neuroendokrini stresni odgovor, anestetike uključujući opioidne analgetike i postoperativnu bol. Najčešće istraživane imunološke stanice su prirodne stanice ubojice (NK) na koje utječu i anesteziološki i kirurški postupak. Pokazano je da ketamin, tiopental, hlapljivi anestetici, fentanilimorfin, ali ne i propofol, remifentanil i tramadol, smanjuju broj cirkulirajućih NK stanica i njihovu citotoksičnost. Razina citotoksičnosti NK stanica obrnuto je proporcionalna stadiju i proširenosti karcinoma. Regionalna anestezija i njezin mogući povoljan učinak na predoperativni imunološki odgovor i dugoročni ishod nakon operacije istraživani su kao alternativa općoj anesteziji u bolesnica koje su podvrgnute operaciji karcinoma dojke. Cilj ovog pregleda literature je procjena utjecaja regionalne anestezije na imunološki odgovor u pacijentica podvrgnutih operaciji karcinoma dojke te njezina usporedba s općom anestezijom.

Ključne riječi: *operacija karcinoma dojke, opća anestezija, regionalna anestezija, imunosupresija, imunološki odgovor*