CONTINUING EDUCATION

Impact of anesthesia on cancer recurrence

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Abstract Surgery remains the mainstay treatment in the majority of solid cancers. Anesthetics and analgesics used during the perioperative period may modulate the innate and adaptive immune system, inflammation and angiogenesis, and have a direct effect on cancer cells that could ultimately modify oncological outcomes. For instance, volatile anesthetics and opioid analgesics have shown predominantly pro-tumor effects, while propofol, non-steroid anti-inflammatory drugs have mostly anticancer effects. Researchers have been especially interested in investigating the association between the use of regional anesthesia techniques and the postoperative survival of patients with cancers. Since the results of the current retrospective studies are conflicting, several researchers are conducting prospective randomized trials.

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PALABRAS CLAVE
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Impacto de la anestesia en la recurrencia de cáncer

Resumen Las intervenciones quirúrgicas siguen siendo el tratamiento de elección de muchos tumores sólidos. Los anestésicos y analgésicos usados en la actualidad tienen efectos en el sistema inmunológico, inflamatorio y angiogénico de los pacientes así como también en células malignas. Los anestésicos inalatorios y los opiáceos tienen un efecto predominantemente protumoral mientras que los agentes anti-inflamatorios no esteroides y propofol parecen tener acciones antitumorales. Es por esto que diferentes grupos de investigadores han tratado de estudiar la posible asociación entre el uso de anestésicos y analgésicos con la supervivencia postoperatoria de pacientes oncológicos. Desafortunadamente, los resultados son controvertidos por lo que estudios prospectivos aleatorios controlados se están llevando acabo en diferentes centros.

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Introduction

Cancer is a global health problem that affects every region and socioeconomic level and its incidence is increasing at an alarming pace due to growth and aging of the population. Malignancies are the second most common cause of death in the United States. Since, surgery still remains as the first-line treatment in the majority of solid cancers; there has been a great interest in the development of perioperative interventions targeted to improve surgical care and prolong the survival of patients.

In patients with significant tumor burden, there is a time lapse between surgery and the start of adjuvant therapy when the so-called minimal residual disease (MRD) can grow because of the combination of 3 factors: (1) inflammation, (2) immune suppression and (3) angiogenesis (Fig. 1). Several studies have demonstrated that all of those factors are tightly interrelated not only in the biology of cancer initiation but also in the pathophysiology of cancer recurrence. Along this line, anesthesiologists, surgeons and other perioperative physicians have been trying to elucidate whether the use of different anesthetics/analgesic drugs or techniques known to modulate inflammation, the immune system and angiogenesis might have an impact on long-term oncological outcomes.

In the present article, we will summarize the current state of understanding on anesthetics–analgesics and their association with oncological outcomes.

Volatile anesthetic agents

Many studies have indicated that volatile anesthetics have actions not only on the immune system, inflammatory pathways and angiogenesis but also on cancer cells (Fig. 2); therefore, it has been speculated that their use in patients undergoing cancer surgery could modulate the growth of the MRD. In the immune system, halogenated anesthetics inhibit directly the function of natural killer (NK) cells and interferon-induced activity of these cells that results in an increase number of metastasis. Volatile anesthetics have also significant anti-inflammatory properties; however, the magnitude of this effect depends on several factors including time of exposure, type of halogenated agent and model of inflammation studied. For instance, sevoflurane and desflurane decrease the local inflammatory response associated with surgery and one-lung ventilation in patients undergoing thoracic surgery without modifying the release of systemic inflammatory markers. Volatile anesthetics modulate angiogenesis as well. This effect appears to be linked to their direct effect on cancer cells. For instance, isoflurane increases the expression of hypoxia-induced factor on renal cancer cells. Volatile anesthetics may also alter apoptotic pathway signaling of cancer cell. Isoflurane exposure of colon cancer cells leads to resistance against apoptosis via a Cav-1-dependent mechanism and it has shown to increase proliferation and invasion in head and neck squamous cell carcinoma cell lines. Huitink et al. found that volatile anesthetics can also modulate human breast and brain tumor cells gene expression in a time-dependent fashion. The authors suggested that their findings could not only have clinical implications but more interestingly they hypothesized that the timing of tumor excision may influence the gene expression levels. On the other hand, positive effects were found for volatile anesthetics: in a study in vitro, sevoflurane and desflurane inhibited mouse colon carcinoma cell migration across simulated extracellular matrix via the decrease of metalloproteinase-9 release; while halothane, isoflurane, and sevoflurane showed cytotoxic effects on different treated human tumor cells, although this phenomenon was not uniform across all the cell lines. Although clinical data in humans is almost inexistent, a recent study that investigated the effect of sevoflurane and desflurane on progression free survival in patients with ovarian cancer demonstrated that women who had tumor reduction under desflurane-based general anesthesia had a significantly longer survival than those treated with sevoflurane.

Intravenous anesthetic agents

Intravenous anesthetics also have actions on the inflammatory and immune system and angiogenesis (Fig. 2). Propofol favors a Th1 response, preserves the function of NK cells, stimulates the cytolytic activity of cytotoxic lymphocytes and decreases angiogenesis, thus favoring a microenvironment capable of tumor cells elimination. In contrast, thiopental favors the balance to the Th2 state and decreases the cytotoxic activity of NK cells, thus promoting a protumoral state. The effects of thiopental on angiogenesis still remain unknown.

Ketamine has shown significant anti-inflammatory effects in different experimental models but it also reduces the number and activity of NK cells, which promotes lung metastases in a rodent model of metastasis formation. The effects of ketamine on angiogenesis are largely unknown, however in rodents, the intravenous infusion of this anesthetic does not appear to affect concentrations of the vascular endothelial growth factor. Dexmedetomidine is a sedative commonly used during surgery, however, its effects on the immune system are largely unknown. In contrast, the actions of dexmedetomidine on inflammation have been the
focused of several investigations suggesting predominantly anti-inflammatory effects.\textsuperscript{17,20}

Propofol, dexmedetomidine and thiopental have also multiple direct effects on cancer cells. Propofol induces apoptosis, suppresses proliferation, cell adhesion, migration and angiogenesis of different cancer cell lines, and it inhibits the production of prostanoids via the suppression of (cyclooxygenase) COX-2 activity.\textsuperscript{16,21-24} In contrast, dexmedetomidine and thiopental have shown to stimulate the proliferation of breast cancer cells and be protective effect against the cytotoxic action of vincristine on pheocromocytoma cells, respectively.\textsuperscript{25,26} The effects of ketamine on cancer cells are largely unknown.

**Local anesthetic drugs**

Overall, local anesthetics (LAs) appear to have anti-inflammatory properties (Fig. 2). For instance, lidocaine inhibits chemokine-induced arrest and transendothelial migration of neutrophils in septic patients.\textsuperscript{27} In a clinical randomized study, Yardeni et al. demonstrate that pericellular and intraoperative intravenous lidocaine produces not only adequate pain relief in the immediate postoperative period, but also caused a significant reduction of the inflammatory response.\textsuperscript{28} LAs also act on cellular mediators of the immune response. Studies have shown that at high concentrations, LAs can suppress the production of interleukin-2, induce apoptosis in T cell death and decrease the function of NK cells.\textsuperscript{29} In contrast, at clinically relevant plasma concentrations, lidocaine stimulates the function of NK cells.\textsuperscript{30} The effects of LAs on angiogenesis have not been well studied; however, experimental data indicate that lidocaine at doses used for infiltrative anesthesia can induce angiogenesis.\textsuperscript{31}

LAs also act on cancer cells in which they can induce apoptosis, decrease their proliferation and diminish invasion although these actions are only observed after high concentrations. A study on human tongue cancer cells indicates that lidocaine inhibits (epidermal growth factor) EGF-stimulated EGFR activity which is referred as a mechanism of antiproliferation.\textsuperscript{32} Different local anesthetics have shown to promote apoptosis in a neuroblastoma cell line.\textsuperscript{33}

**Opioids**

Opioids are the most commonly used analgesics in the perioperative period. The \(\mu\)-opioid receptor (MOR) is expressed in malignant and non-malignant cells. In the immune system, opioids are predominantly immune suppressive; however, it is worth remembering that this effect depends on the opioid type, amount and experimental condition.\textsuperscript{34} Opioids also modulate inflammation. For instance, morphine induces a switch from macrophage type M1 to M2 in a model of incisional pain. Interestingly, this phenomenon coincides with an increase in the expression of COX-2 in macrophages.\textsuperscript{35}

Opioids activate MOR promoting tumor growth and metastasis pathways (Fig. 2).\textsuperscript{36} Different investigators have demonstrated in non-small cell lung cancer cells that opioids facilitate endothelial–mesenchymal transformation, a step needed for cancer cells to become invasive.\textsuperscript{37} In line with this effect of opioids in non-small cell lung cancer, the use of opioids in the intraoperative period has been associated reduced survival after lung cancer surgery.\textsuperscript{38} Yet, positive effects of opioids have been reposted by Sasamura et al. who showed in a mouse model of cancer pain that analgesic doses of morphine markedly suppressed the growth and metastasis of tumor cells.\textsuperscript{39}

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

During the perioperative period, the progression of cancer is clearly linked to a state of increased angiogenesis, exaggerated inflammation and strong immune suppression.\textsuperscript{40} Among the many pro-inflammatory mediators prostaglandins (PG), specially PGE\textsubscript{2}, induce epithelial cell proliferation, inhibition of apoptosis and stimulation of angiogenesis.\textsuperscript{41} PGE\textsubscript{2}
has also direct effects on the immune system; it inhibits NK cells cytotoxicity, and also suppresses the adaptive immune system by the induction of CD8+ T cells apoptosis and the inhibition of dendritic cell maturation, thus resulting in the abortive activation of naive CD8+ T cells. 42–44 Experimental data clearly demonstrate that overexpression of the enzyme COX-2 is linked to invasion and metastasis formation 45. Based on this premise, it has been hypothesized that the use of COX inhibitors during the perioperative period could improve survival of cancer patients by diminishing inflammation and immune supression. Along this evidence, Forget et al. have demonstrated in a cohort study that the use of ketorolac during cancer surgery was associated with lower risk of metastasis longer survival. 46

Regional anesthesia

An increasing interest has been recently put on whether regional anesthesia/analgesia could improve survival outcomes after oncological surgery. 47 Experimental studies in animals demonstrated how the addition of spinal block to general anesthesia during laparotomy surgery positively impact the tumoricidal activity of liver mononuclear cells and decreased metastasis. 48, 49 Although a meta-analysis could not find any significant difference between the effect of neuraxial regional anesthesia and general anesthesia on postoperative natural killer T lymphocyte function, the authors postulated that the results may have been affected by a high heterogeneity among studies. 50 A pilot study, part of an ongoing prospective randomized trial (NCT00418457), 51 investigated the effect of serum from women undergoing breast cancer surgery on the function of NK cells from healthy subjects and found that the serum from women who received propofol–paravertebral block led to greater NK cell cytotoxicity in vitro than the serum from women who received sevoflurane–opioid general anesthesia.

Whether the potential beneficial effects of regional anesthesia/analgesia translate into longer cancer-related survival it is still debatable. A meta-analysis, conducted by Chen and Miao, 52 combined 18 studies of different types of cancer and failed to show an association between the use of regional anesthesia/analgesia and improved recurrence-free and cancer-specific survival, yet it was observed to improve overall survival. However, it is worth mentioning that this meta-analysis had several limitations including (a) that the studies reported in the analysis were retrospective, (b) different anesthesia and analgesia techniques were used in the different studies, (c) the definitions of outcomes were not the same in all studies and (d) different malignancies and tumor staging were grouped in the analysis. Prospective randomized controlled trials are needed to properly assess whether there is a causative relation between neuraxial anesthesia/analgesia and a lower risk of cancer recurrence and improved survival. The Outcomes Research Consortium (Cleveland Clinic, USA) is performing two multicenter controlled trials one in breast cancer surgery (NCT00418457) and the other one in laparoscopic colorectal cancer surgery (NCT00684229). 53

In conclusion, volatile anesthetics, opioids, local anesthetics and NSAIDs have all demonstrated to, directly or indirectly, be able to affect the proliferation, epithelial–mesenchymal transition and invasion properties of cancer cells as well as different elements of the tumor microenvironment. However, none of these drugs has shown a direct cause–effect relationship between their use in the perioperative period and a reduction in cancer recurrence or increase in cancer-specific survival. Even though clinical studies have been showing conflicting results, it is important to continue developing high-quality prospective clinical trials in order to determine whether anesthesia/analgesia techniques during the perioperative period have an impact on cancer outcomes.

Conflict of interest

Los autores declaran no tener ningún conflicto de intereses.

References


