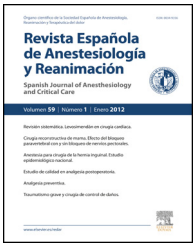
Rev Esp Anestesiol Reanim. 2015;62(10):570–575

Revista Española de Anestesiología y Reanimación

www.elsevier.es/redar



CONTINUING EDUCATION

Impact of anesthesia on cancer recurrence☆

B.M. Lee[a], J.P. Cata[a,b,*]

[a] *Department of Anaesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Cancer, Houston, TX, USA*
[b] *Anesthesia and Surgical Oncological Research Group, TX, USA*

Received 24 February 2015; accepted 2 April 2015
Available online 27 May 2015

KEYWORDS
Neoplasms;
Recurrence;
Inflammation;
Angiogenesis;
Anesthesia

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.

PALABRAS CLAVE
Neoplasia;
Recurrencia;
Inflamación;
Angiogenesis;
Anestesia

Impacto de la anestesia en la recurrencia de cáncer

Resumen Las intervenciones quirúrgicas siguen siendo el tratamiento de elección de muchos tumores solidos. 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 tiene un efecto predominantemente protumoral mientras que los agentes anti-inflamatorios no esteroideos 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.

☆ This article is part of the Anaesthesiology and Resuscitation Continuing Medical Education Program. An evaluation of the questions on this article can be made through the Internet by accessing the Education Section of the following web page: www.elsevier.es/redar.

* Corresponding author.
E-mail address: jcata@mdanderson.org (J.P. Cata).

http://dx.doi.org/10.1016/j.redar.2015.04.003

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.[1] 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.[2] 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.[3] 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 hypoxible-induced factor on renal cancer cells.[4] 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.[5,6] Huitink et al.[7] 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[8]; 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.[9] 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.[10]

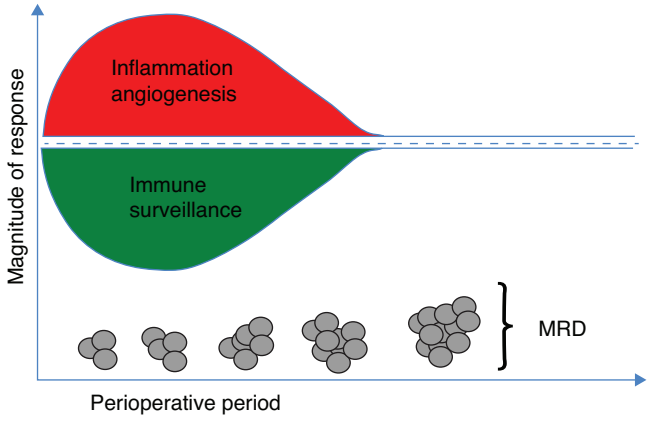


Figure 1 MRD growth in the perioperative period. The figure demonstrates the 3 mechanisms behind MRD growth in the perioperative period. Anesthetics and analgesics can all modify inflammation, immune suppression and angiogenesis. MRD: minimal residual disease

Intravenous anesthetic agents

Intravenous anesthetics also have actions on the inflammatory and immune system and on 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 microenviroment capable of tumor cells elimination.[11–16] In contrast, thiopental favors the balance to the Th2 state and decreases the cytotoxic activity of NK cells, thus promoting a protumoral state.[11] 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.[14,17,18] 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