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The Effects Of Propofol Versus Sevoflurane In Surgical Lung Cancer Patients

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Abstract

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer. Lung cancer leads all cancer death rates worldwide. Surgical treatment for NSCLC warrants a role for the anesthetist to influence recurrence-free survival, overall survivability, and overall mortality. Literature suggests propofol and sevoflurane are linked to immunosuppressive characteristics by decreasing immunity via different mechanisms. Propofol has known anti-inflammatory effects, but studies reveal sevoflurane has similar capabilities. Sevoflurane may attenuate the metastatic potential of lung cancer by stopping platelet activation, but sevoflurane may also enhance other pathways of metastasis. Similarly, propofol has anti-metastatic abilities, hindering angiogenesis by downregulating necessary growth factors. Propofol and sevoflurane influence various NSCLC growth and metastasis mechanisms, but research is inconclusive on how propofol or sevoflurane definitively affects outcomes with NSCLC. Heterogenous clinical evidence supports a propofol TIVA for improved recurrence-free survivability, increased overall survivability, and decreased overall mortality more than inhalation anesthetics. Ultimately, more research is needed to justify the preferred anesthetic.

Keywords: propofol, sevoflurane, lung neoplasm, lung cancer

The Effects of Propofol Versus Sevoflurane in Surgical Lung Cancer Patients

Lung cancer leads all cancer death rates worldwide (Yamaguchi et al., 2021). According to the National Cancer Institute (NCI) (2021), more people will die from lung cancer than breast, prostate, and colorectal cancers combined. While there are multiple types of lung cancer, non-small cell lung cancer (NSCLC) accounts for nearly 85% of diagnosed lung cancers (Midthun, 2021). As in the case of many cancers, smoking cigarettes is the leading risk factor for the pathogenesis of NSCLC (Norris, 2018). In fact, smoking is the cause of up to 80% of NSCLC (Norris, 2018). Other risk factors include ionizing radiation, asbestos, and radon gas(Hines & Marschall, 2017). Due to NSCLC's relative insensitivity to chemotherapeutic measures, surgical treatment is typically warranted, especially in the early stages of the disease (Midthun, 2021). Overall, lung cancer's 5-year relative survival rate is 21.7%. However, in its early localized stage with surgical resection, the prognosis is best at nearly 60% (NCI, 2021).

NSCLC has multiple histological subtypes, including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (Hines & Marschall, 2017; Midthun, 2021; Norris, 2018). Squamous cell carcinomas begin in the intraluminal major bronchi and frequently spread to the hilar lymph nodes (Hines & Marschall, 2017; Norris, 2018). These malignant cells are typically confirmed via cytological analysis of the sputum (Hines & Marschall, 2017; Norris, 2018). By contrast, adenocarcinoma originates in the peripheral bronchiolar and alveolar tissue (Hines & Marschall, 2017; Norris, 2018). Adenocarcinoma may be more challenging to diagnose due to its location, which requires invasive diagnostic procedures. Additionally, the site of adenocarcinoma also presents challenges when differentiating adenocarcinoma from other lung lesions via radiological imaging. Like adenocarcinomas, large cell carcinomas begin in the peripheral bronchial tree but as a large and anaplastic tumor (Norris, 2018). Fortunately, with

each of these subtypes, early detection paired with surgical intervention increases the chance of survival and reduces the possibility of metastasis.

Since NSCLC treatment frequently warrants surgical intervention, most medications, including general anesthetics, are short-acting, allowing a fair amount of control in optimizing the anesthetic management without overcorrecting and attenuating the body's homeostatic processes. Therefore, unless sentinel events occur, long-term consequences are not typically characteristic of anesthesia outcomes.

Conventionally, general anesthesia is maintained by a volatile halogenated inhalation agent, such as sevoflurane. In recent decades, propofol combined with IV analgesics or regional blocks has allowed the possibility of administering total intervenous anesthesia (TIVA).

Use of Propofol

Propofol is an intravenous hypnotic utilized as a general anesthetic. Propofol's primary mechanism of action is as a gamma-aminobutyric acid subunit A (GABA-$_A$) agonist (Hines & Marschall, 2017). By stimulating the GABA-$_A$ receptor, the neurons' cell membranes become hyperpolarized, thus preventing the creation of action potentials from propagating messages (Nagelhout & Plaus, 2013). Propofol can induce rapid unconsciousness due to its immediate intravenous bioavailability, reaching peak brain concentration levels in less than a minute (Hines & Marschall, 2017). Propofol's high lipid solubility supports rapid redistribution from the brain to adipose tissue (Hines & Marschall, 2017; Nagelhout & Plaus, 2013). The consequence of the rapid redistribution of the active drug is a very short duration of action. Therefore, a continuous intravenous propofol infusion is needed to maintain general anesthesia.

TIVA was made possible over time with the advent, availability, and lowering cost of propofol. Thus, TIVA became a feasible alternative to volatile inhalation agents to maintain

anesthesia in the intraoperative period. Since propofol lacks any analgesic properties, it is frequently paired with intravenous analgesics and regional anesthesia to provide a complete anesthetic.

Recent research has investigated propofol's antioxidant, anti-inflammatory, and possible antitumorigenic properties. Propofol can work as a free radical scavenger (Hines & Marschall, 2017; Nagelhout & Plaus, 2013). Free radicals are reactive molecules that may be byproducts of biological processes or external exposures, such as radiation (Hines & Marschall, 2017). However, these molecules are not benign as they can disrupt genetic components that may cause cancer. Animal trials have linked propofol to promoting natural killer cells' cytotoxic activity, thus possibly allowing the robust innate immune system to function more efficiently by preventing cancer cell metastasis in breast cancer (Sherwin et al., 2021). Additionally, in vitro gastric cancer cell line experiments demonstrate inhibition of cell proliferation, invasion, and migration, in the presence of propofol (Sherwin et al., 2021). While these advantageous characteristics of propofol appear promising to improve outcomes for NSCLC surgical patients, propofol has been linked to negatively affecting the adaptive immune system.

Use of Sevoflurane

Sevoflurane is an inhaled volatile anesthetic. Like propofol, sevoflurane agonizes and stimulates the inhibitory GABA-$_A$ receptor (Nagelhout & Plaus, 2013). Moreover, sevoflurane stimulates other inhibitory pathways, including glycine receptors and potassium channels. Essential for maintaining general anesthesia, sevoflurane antagonizes the N-methyl-D-aspartate (NMDA) receptors to prevent glutamate binding, an excitatory neurotransmitter (Nagelhout & Plaus, 2013). If stimulated, the NMDA receptor increases the cell's response to surgical

stimulation and decreases endogenous opioids' pain-relieving effects on opioid receptors (Hines & Marschall, 2017; Nagelhout & Plaus, 2013).

Additionally, sevoflurane inhibits other stimulatory pathways, such as the nicotinic receptors, sodium channels, and dendritic spine function and motility (Nagelhout & Plaus, 2013). Although sevoflurane has multiple mechanisms of action to provide a general anesthetic, sevoflurane is frequently paired with intravenous analgesics and regional anesthesia to reduce consequences associated with the autonomic response seen with the solitary use of inhalation anesthetics. Otherwise, without these analgesic adjuncts, an anesthetist may have to increase the minimum alveolar concentration (MAC) of sevoflurane to 1.5, which could have drastic autonomic response consequences (Barash et al., 2017).

Initial research on sevoflurane's effect on cancer cells may implicate the possibility of increasing metastatic spread and impeding the body's immune system (Sherwin et al., 2021). Some proposed mechanisms include the ability to upregulate oncogenic genes (Sherwin et al., 2021). These genes may facilitate the growth of cancer cells by increasing angiogenesis for malignant cells (Sherwin et al., 2021). In contrast, some research has shown sevoflurane may have cytoprotective effects on healthy cells by preventing malignant cell functions for growth (Sherwin et al., 2021).

Literature Review and Analysis

Methods

A literature search was accomplished through the University of New England Library Services Portal with the following databases: EBSCO host, CINAHL Complete, Cochrane Collection Plus, Embase, and Pubmed. Keywords executed in each database included the following: propofol, sevoflurane, lung neoplasm, and lung cancer. Inclusion criteria were limited

to peer-reviewed articles published from 2016 until 2021, English language, full portable

document format, and adults aged 18-99. If the full text was unavailable, Google Scholar was

utilized to locate the entire document. UpToDate was used to support identified articles with

additional sources of current and peer-reviewed evidence-based practice guidelines.

Adaptive Immunity

One component of the adaptive immune system are T lymphocytes. There are multiple

subsets of T lymphocytes (Nagelhout & Plaus, 2013). The cluster of differentiation 3 (CD3) T

cells are mature T lymphocytes that can activate helper T cells (Th) and cytotoxic T lymphocytes

(CTLs), thus creating an immune response to fight invasion (Heimall, 2020). Th cells secrete

cytokines to activate and recruit CTLs (Nagelhout & Plaus, 2013). CTLs release cytotoxic

perforins to destroy infected or malignant cells (Nagelhout & Plaus, 2013). Lastly, regulatory T

lymphocytes (Treg) modulate the immune response by suppressing T cell proliferation and

downregulating Th cells (Nagelhout & Plaus, 2013).

Research reveals conflicting information on general anesthetics' immunosuppressive

properties on the adaptive and innate immune system, which may indirectly permit the growth

and proliferation of cancer cells. Perioperative immunosuppression by various anesthetic agents

may attenuate the body's ability to combat cancer growth and expansion. Yamaguchi et al.

(2021) conducted a randomized controlled trial (RCT) to determine the relationship between

perioperative immunosuppression and anesthetic agents, including desflurane, sevoflurane, and

propofol. The researchers separated 64 lung cancer patients into three groups receiving these

anesthetics. Yamaguchi et al. compared peripheral blood samples drawn before induction and at

the end of surgery to compute the numbers of Th, CTLs, programmed death on Th and CTLs,

and Tregs by flow cytometry. The results revealed the propofol group decreased the number of

CTLs after surgery more than the desflurane and sevoflurane groups. Since CTLs have cancer-fighting cytotoxicity, the authors theorize that a lower CTL count may increase cancer recurrence risk. Additionally, the sevoflurane group increased Tregs after surgery, which is responsible for the death and suppression of CTLs (Yamaguchi et al., 2021). Therefore, inhalation anesthetics and propofol may support the growth and proliferation of lung cancer cells with two different mechanisms.

Fu et al. (2018) evaluated similar lymphocyte counts during lung cancer resection surgery with nearly double the study subjects by Yamaguchi et al. (2021). The subjects were randomly and equally divided into a group receiving propofol and remifentanil versus a group receiving propofol and regional anesthesia. Specifically, the researchers measured CD3 T lymphocytes, Th cells, and Tregs at multiple periods perioperatively. Cytometry by Fu et al. revealed an overall decrease in CD3, Th, and Tregs lymphocyte counts in both groups. But, the combined propofol and regional anesthesia group had significantly and consistently higher CD3, Th, and Tregs lymphocyte counts than the propofol and remifentanil group up to 72 hours after surgery.

Although the researchers did not compare propofol to sevoflurane, propofol may have a dose-dependent effect in decreasing these particular lymphocytes since remifentanil was used by both Fu et al. (2018) and Yamaguchi et al. (2021). Furthermore, the combination of both studies reveals propofol can decrease various cells of the adaptive cellular immune system; thus, propofol possibly exacerbates a void in the immune system when the system is already taxed by surgical stress – increasing vulnerability and susceptibility to cancer cell invasion and proliferation. Limitations include being a single-center study and not evaluating the effects of opioids on these particular immunity markers. Similarly, both studies only assessed the quantity and not the qualitative cellular function of these lymphocytes.

Innate Immunity

Natural killer (NK) cells are components of innate immunity that are affected by general anesthetics. NK cells have unique cytotoxic abilities against their host cells that become compromised by cancer cells or viruses (Johnston, 2021). These innate immune cells recognize healthy host cells by major histocompatibility complex (MHC) class I molecules (Jeon et al., 2020; Johnston, 2021). MHC class I molecules are typically downregulated when cells become malignant (Johnston, 2021). If this occurs, the NK cell will be unable to bind to the MHC I receptor. The NK cell will activate and release cytotoxic, granulated perforins to disrupt the target cell's membrane and induce apoptosis (Johnston, 2021).

Preliminary studies link the suppression of NK cells' cytotoxicity with sevoflurane. Jeon et al. (2020) performed an in vitro quasi-experimental analysis to determine if a dose-dependent sevoflurane concentration could alter NK or NSCLC cell function. The researchers exposed human NSCLC cells to various concentrations (0, 12.5, 25, 50, 100, and 200 µM) of sevoflurane solution for 6 hours. Results revealed sevoflurane decreased the expression of natural killer receptor group 2, member D (NKG2D), at the highest dose (200 µM) of sevoflurane. NKG2D is a cell surface receptor on NK cells that binds to cancer cells' ligands to activate NK cells' cytotoxic effects (Jeon et al., 2020). Even though the NKG2D expression was suppressed at 200 µM of sevoflurane, lower doses at 100 µM or less were surprisingly associated with increased NKG2D expression (Jeon et al., 2020). Therefore, lower doses of sevoflurane may not be harmful to NK cells' cytotoxic activity.

This study has several limitations. Most importantly, Jeon et al. (2020) conducted an in vitro study that cannot prove direct human application. Furthermore, without understanding the exact mechanism for the decreased NKG2D expression from 200 µM of sevoflurane, other

synthetic materials and preservatives not in humans may have influenced these results. Finally, the NSCLC cells were treated with sevoflurane for 6 hours to compensate for evaporation. Typical lung resection cases may not last as long nor warrant 200 µM of arterial sevoflurane concentration.

Effect on Inflammatory Mediators

Inflammatory responses to surgical trauma and mechanical ventilation can impair physiological processes. Consequently, this may jeopardize the prognosis of patients postoperatively (Chen et al., 2020; Tian et al., 2017). Inflammation can promote malignancy by further damaging tissue and cells (Heimall, 2020). Recent studies have evaluated the effects of general anesthetics on inflammation. In an RCT, Tian et al. (2017) discovered how propofol could reduce the perioperative inflammatory response better than sevoflurane in lung cancer patients undergoing a lobectomy. The researchers randomly and equally divided 62 lung cancer patients into a propofol and sevoflurane group. The researchers evaluated arterial blood for interleukin-6 (IL-6), a proinflammatory cytokine, and interleukin-10 (IL-10), an anti-inflammatory cytokine, before induction, before one-lung ventilation, after sternal closure, and 24 hours postoperatively (Heimall, 2020; Tian et al., 2017). After induction and through 24 hours postoperatively, both groups had a significant increase in IL-6 and a decrease in IL-10. However, the propofol group had an overall lower IL-6 and higher IL-10 than the sevoflurane group during the same period.

Conversely, Chen et al. (2020) performed an RCT equally dividing 168 lung cancer patients receiving a lobectomy into a propofol and sevoflurane group. Similar to Tian et al. (2017), researchers induced their sevoflurane group with 8% sevoflurane and then collected arterial blood to monitor IL-6 and tumor necrosis factor-alpha (TNF-alpha) at the beginning of

single-lung ventilation, beginning of double-lung ventilation, and 30 minutes after double-lung

ventilation. Findings revealed no significant difference in levels of IL-6 and TNF-alpha from the

beginning of single-lung ventilation to the beginning of double-lung ventilation in both groups

(Chen et al., 2020). However, 30 minutes after double-lung ventilation, Chen et al. found that the

sevoflurane group had lower levels of IL-6 and TNF-alpha compared to the propofol group.

Thus, in contrast to Tian et al., Chen et al. theorize sevoflurane substantially reduces the

inflammatory response in lung cancer patients receiving a lobectomy.

Furthermore, Chen et al. (2020) hypothesize sevoflurane may increase heme oxygenase

1, an enzyme for heme degradation. The increase of heme oxygenase 1 may explain the

mechanism for some of the possible anti-inflammatory, anti-oxidative, anti-proliferative, and

anti-apoptotic properties of sevoflurane (Chen et al., 2020).

Effect on Metastasis

Early surgical intervention is vital to prevent the continuing development and ultimate

spread of NSCLC. Unfortunately, surgery may exacerbate the metastatic potential and increase

the circulating volume of tumor cells (Liang et al., 2016). Increasing circulating tumor cells and

their metastatic capabilities may be related to increased platelet activation, evasion of the host

immune system recognition, displacement during surgical manipulation, and increasing growth

factors (Fares et al., 2020; Sherwin et al., 2021).

Platelet Activation

Cancer patients typically exhibit more upregulation of activated platelets than non-

cancerous individuals (Liang et al., 2016). Furthermore, surgical stress potentiates platelet

activation (Liang et al., 2016). Circulating tumor cells interact with activated platelets to form a

protective coating around the tumor cells to prevent detection by the immune system (Fares et

al., 2020). Therefore, surgical procedures on a cancer patient may create beneficial conditions for cancer cells to metastasize and proliferate.

Research suggests sevoflurane may suppress platelet activity. Liang et al. (2016) conducted an in vivo RCT on 46 lung cancer patients undergoing an elective video-assisted thoracoscopic surgery (VATS) to determine the effects of sevoflurane and isoflurane on platelet activation. The researchers randomized equal numbers of patients into an isoflurane and sevoflurane group. They performed a standardized method of anesthesia during VATS, including controlled use of propofol and remifentanil for maintenance adjunct. The authors evaluated platelet activation by detecting the expression of glycoprotein IIb/IIIa, P-selectin, and platelet aggregation rate via peripheral blood samples drawn 10 minutes before anesthesia, 1 hour after the start of surgery, and 1 hour postoperatively.

Liang et al. (2016) found no significant difference in glycoprotein IIb/IIIa or P-selectin levels at baseline between groups. However, the researchers revealed both groups' glycoprotein IIb/IIIa levels increased intraoperatively and postoperatively, with the isoflurane increasing more than the sevoflurane group. Similarly, the authors found both groups had markedly increased P-selectin levels intraoperatively and postoperatively, with the isoflurane group also increasing more than the sevoflurane group. Lastly, the platelet aggregation rate in both groups was increased intraoperatively and postoperatively, with the isoflurane group again increasing more than the sevoflurane group. Therefore, surgery causes increased platelet activation, but sevoflurane helps inhibit platelet activation significantly more than isoflurane (Liang et al., 2016). Furthermore, sevoflurane's inhibitory effect on platelet activation may decrease NSCLC's ability to metastasize.

Additionally, Liang et al. (2016) performed an in vitro experiment on human lung adenocarcinoma cells to determine if the anesthetics can reduce the platelet-induced invasion of lung cancer cells. The authors used blood from 6 lung cancer patients receiving isoflurane at the beginning of surgery and 1 hour postoperatively; the isoflurane patients had higher platelet activity (increases cancer cell invasion) postoperatively than sevoflurane. The isolated platelets activated after surgery were treated with sevoflurane, isoflurane, or neither for 4 hours. Liang et al. found that sevoflurane-treated platelets activated after surgery were reduced. In contrast, isoflurane could not suppress platelet-induced invasion compared to the untreated platelets activated after surgery. The authors further evaluated the sevoflurane and isoflurane platelets activated after surgery. They found that the sevoflurane treated platelets activated after surgery had markedly decreased glycoprotein IIb/IIIa, P-selectin, and platelet aggregation rate levels compared to the isoflurane group. Thus, Liang et al. contributed the inhibited platelet activation mechanism to lowering glycoprotein IIb/IIIa, P-selectin, and platelet aggregation rate.

Matrix Metalloproteinase Expression

Jeon et al. (2020) suggest that sevoflurane increases the expression of matrix metalloproteinases (MMPs), specifically MMP-1, -2, and -9. MMPs remove NKG2D receptors from the cellular surface of cancer cells. MMPs allow the malignant cells to evade recognition from NK cells' cytotoxic actions (Jeon et al., 2020). Furthermore, MMPs will degrade the extracellular matrix, promoting a favorable environment for cancer cell angiogenesis, invasion, migration, and ultimate metastasis (Jeon et al., 2020). Similarly, Tian et al. (2017) provided evidence of increasing MMP-9 expression after induction using sevoflurane versus propofol during lobectomy. Therefore, the in vitro experimental results of MMP-9 by Jeon et al. are consistent with the human RCT by Tian et al.

On the other hand, Chen et al. (2020) revealed sevoflurane reduced the concentration of MMP-9 more than propofol in their human RCT when monitoring inflammatory markers. Although Jeon et al. (2020) linked high dose sevoflurane (200 µM) with upregulation of MMP-9 expression in vitro, Chen et al. revealed sevoflurane has lower MMP-9 expression than propofol in vivo. This may explain why the arterial blood concentration of sevoflurane did not reach 200 µM in the trial by Chen et al. Regardless, the results provided by Chen et al. and Tian et al. conflict with each other when comparing the effect of sevoflurane and propofol on MMP-9 expression. Multi-center RCTs with a larger sample size are warranted to understand further the behavior of sevoflurane and propofol on MMP-9 expression.

Growth Factors

Tumor cells' survival and metastasis typically depend on the ability to continue to grow by increasing their blood supply through angiogenesis. If tumor cells do not have enough blood supply, they upregulate hypoxia-inducible factor 1-alpha (HIF1A) to activate the expression of vascular endothelial growth factor (VGEF) (Sherwin et al., 2021). VGEF promotes angiogenesis, remodeling of lymphatic pathways, and mitotic NSCLC division (Sen et al., 2019). In addition, tumor cells utilize transforming growth factor-beta (TGF-beta), an oncogenic cytokine, to promote the growth of NSCLC cells by increasing VGEF expression and causing immunosuppression (Sen et al., 2019; Sherwin et al., 2021). This pathway supports tumorigenesis and ultimately increases the likelihood of metastasis (Sen et al., 2019; Sherwin et al., 2021).

Research has correlated propofol with lower serum growth factor levels in patients receiving VATS for radical NSCLC resection. Sen et al. (2019) conducted an RCT on 90 NSCLC patients having a radical NSCLC resection. The researcher randomly divided subjects

into a sevoflurane and a propofol with regional anesthesia group. The propofol with regional

anesthesia group received a nerve block preoperatively, and anesthesia was maintained with a

propofol infusion. The sevoflurane group did not receive a nerve block and was maintained by

sevoflurane alone. Blood samples were collected before surgery and 24 hours postoperatively to

measure the serum VEGF and TGF-beta levels. After serum analysis, Sen et al. found no

significant differences in levels before surgery. But, the VEGF and TGF-beta levels in the

propofol with regional anesthesia group were lower than in the sevoflurane group. The authors'

research correlates how a nerve block and propofol anesthesia can lower the elevation of TGF-

beta and VEGF in patients receiving a VATS for radical NSCLC reaction.

   Although Sen et al. (2019) correlate mechanisms for NSCLC growth and metastasis,

limitations of this study include clinical correlation does not provide causative evidence that

lowering of TGF-beta and VEGF with the use of propofol with regional anesthesia will prevent

or decrease the risk of further NSCLC growth or metastasis. Likewise, this study also cannot

conclude whether the propofol, nerve block, or combination of both lowered these growth

factors. Prospective, long-range research is warranted to determine how various combinations of

anesthetics influence NSCLC growth or metastasis.

Cancer Recurrence and Mortality

   Many cancer deaths can be attributed to metastatic disease recurrence. Even though

NSCLC surgical candidates often receive radical resection to remove the malignant tumor,

recurrent NSCLC can occur in up to 41% of patients within a year (Midthun, 2021). Tragically,

the median survival of recurrent NSCLC patients may only be up to 8.1 months (Midthun, 2021).

However, studies have correlated TIVA with decreased overall mortality and prolonged

recurrence-free survival compared to inhalation anesthetics (Soltanizadeh et al., 2017; Yap et al.,

2019).

Cancer Recurrence

A meta-analysis published by Yap et al. (2019) explored the impact of general anesthetics

on recurrence-free survival and overall survivability of surgical cancer patients. The researchers

used one RCT and five retrospective studies to examine the effects of propofol TIVA and

inhalation agents on recurrence-free survival in 7,866 breast, esophageal, and NSCLC patients.

The study demonstrated the TIVA group had better recurrence-free survival rates than the

inhalation agents group (Yap et al., 2019). Additionally, Yap et al. used seven retrospective

studies and one RCT to compare the effects of propofol TIVA and inhalation agents on the

overall survivability of 18,778 breast, colorectal, gastric, esophageal, NSCLC, and mixed cancer

patients. Similarly, researchers found a higher overall survival with the TIVA group when

compared to the inhalation agents group (Yap et al., 2019).

Overall Mortality

Propofol TIVA versus inhalation anesthetics may be the optimal choice in various cancer

surgeries for an overall decrease in mortality and prolonged recurrence-free survival

(Soltanizadeh et al., 2017). Soltanizadeh et al. (2017) conducted a systematic review examining

overall mortality and postoperative complications of patients undergoing primary cancer surgery

with a propofol TIVA or inhalation anesthetic. Eight studies with 10,696 patients were included.

Amongst the eight studies, the authors note multiple cancer sites, including urologic,

gastrointestinal, gynecologic, soft tissue, head and neck, breast, and respiratory. Four of the eight

studies compared the overall mortality ranging from 2.66 to 5 years between inhalation agents

and TIVA. The most extensive retrospective study representing 7,030 subjects with various

cancers found increased overall mortality in the inhalation anesthesia group. Alternatively, the

second-largest retrospective study representing 2,838 patients found no significant difference in

overall mortality for breast, colon, or rectum cancers. However, when the researchers combined

all cancer subjects, the overall cancer-related mortality decreased in the TIVA group. The third

retrospective study represented 325 breast cancer subjects with no significant difference in

overall mortality; however, the TIVA group demonstrated a prolonged recurrence-free survival.

Lastly, the only RCT measuring mortality representing 28 bladder cancer patients revealed a

36% versus 14% mortality rate for the inhalation versus TIVA groups.

Although this study provided a large sample size, researchers evaluated patients

undergoing multiple surgeries for various cancers. Thus, the heterogeneity of the surgeries does

not allow direct comparison. Additionally, most patients were enrolled in retrospective studies

vulnerable to selection bias. Lastly, Soltanizadeh et al. (2017) proposed that the results may be

more favorable to the TIVA group due to a shift in using TIVA for more hemodynamically

stable patients versus inhalation anesthetics for hemodynamically unstable and recurrent surgical

patients.

Discussion

GA Effects on the Immune System and Inflammatory Mediators

Even with a controlled anesthetic, surgical tissue trauma causes the release of

catecholamines. It stimulates the hypothalamic-pituitary axis to release corticotropin, causing the

release of cortisol from the adrenal cortex (Hines & Marschall, 2017). This stress response

triggers an immune response because regulatory T cells and other immune cells possess β2-

adrenergic and glucocorticoid receptors (Hines & Marschall, 2017). Activation of these receptors

results in the net release of pro-inflammatory cytokines, such as IL-6 and TNF-α (Hines &

Marschall, 2017). TNF-α is a cytokine released by macrophages, T cells, and NK cells (Heimall, 2020). TNF-α has many functions, including responding to areas where IL-6 has been released to aid proinflammatory processes, such as inducing fever, apoptosis, and inflammation (Heimall, 2020). The release of these cytokines provides positive feedback for the hypothalamic-pituitary axis (Hines & Marschall, 2017). This immune response increases vulnerability to the proliferation of tumor cells (Hines & Marschall, 2017).

With conflicting results from Tian et al. (2017) and Chen et al. (2020), identifying a preferred anesthetic to decrease IL-6 and other proinflammatory markers in lung cancer patients undergoing lobectomy is inconclusive. Both studies were single-center RCTs; however, Chen et al. evaluated nearly triple the subjects of Tian et al. Despite Tian et al. having a smaller sample size, researchers monitored their patients' inflammatory markers more frequently and over a longer time duration. Interestingly, Tian et al. induced the sevoflurane group with 8% sevoflurane, and thus they received no propofol throughout the case.

Comparative studies by Yamaguchi et al. (2021) and Fu et al. (2018) determined that sevoflurane and propofol may negatively affect the adaptive immune system. Yamaguchi et al. and Fu et al. revealed that propofol reduces the CTLs more than sevoflurane. Reducing CTLs responsible for destroying malignant cells directly hinders the body's natural defense system for protecting its host from cancer cell proliferation and invasion. It is vital to understand that Fu et al. linked propofol alone to decreasing most of the T cells, including the CD3, Th, and Tregs. Unfortunately, the decreased count was not compared to sevoflurane. Yamaguchi et al. revealed sevoflurane increases Tregs. This will indirectly reduce the CTLs and Th cells. Ultimately, sevoflurane and propofol will impair the adaptive immune response.

Sevoflurane appears to reduce NK cell activity and quantity and lymphocyte proliferation (Nagelhout & Plaus, 2013). Jeon et al. (2020) demonstrated sevoflurane has a considerable dose-dependent reduction in NK cell expression at 200 µM of arterial sevoflurane. The arterial sevoflurane concentration is between 100 to 300 µM during a balanced sevoflurane anesthetic (Jeon et al., 2020). On the other hand, lower concentrations of sevoflurane may increase NK expression (Jeon et al., 2020). Unfortunately, there were no comparative studies on the impacts of propofol on NK cell expression. Finally, surgical stimulation may also suppress NK cell activity and CTLs (Hines & Marschall, 2017). This results from the activation of the hypothalamic-pituitary axis and autonomic nervous system (Hines & Marschall, 2017).

GA Effects on Metastasis

The ability of the body to prevent the spread of NSCLC is crucial to the overall survival and recurrence rates. Cancer cells use multiple mechanisms to evade and metastasize. Specific mechanisms identified by experiments involving NSCLC were platelet activation, MMP expression, and growth factor regulation. NSCLC cells use platelet activation to protect themselves from the immune system's attacks. This cytoprotective strategy may increase the possibility of NSCLC cells metastasizing. Compared to other volatile anesthetics, Liang et al. (2016) found that sevoflurane lowered glycoprotein IIb/IIIa and P-selectin levels. Glycoprotein IIb/IIIa is a platelet receptor required for activation and adherence to fibrinogen (Abrams, 2021). P-selectin functions as a cell adhesion molecule for lung cancer cells to adhere to platelets and endothelial cells and ultimately move into the vascular compartment (Abrams, 2021; Liang et al., 2016). Thus, the work performed by Liang et al. suggests sevoflurane can attenuate the platelet activation more than other volatiles.

Conclusion

Even though multiple sources link the effects of propofol and sevoflurane to the various mechanisms of NSCLC growth and metastasis, the research is inconclusive as to how propofol or sevoflurane can definitively affect recurrence-free survival outcomes with NSCLC. Literature suggests propofol and sevoflurane are linked to immunosuppressive characteristics by decreasing CTLs via different mechanisms. Furthermore, high-dose sevoflurane may decrease NK cells' cytotoxic potential by reducing the expression of necessary receptors that bind to NSCLC cells. Additionally, studies support propofol's anti-inflammatory effects due to lowering pro-inflammatory IL-6 and increasing anti-inflammatory IL-10 cytokines more than sevoflurane. Yet, other evidence theorizes sevoflurane also has anti-inflammatory capabilities with even lower IL-6 levels and TNF-alpha postoperatively compared to propofol.

Similarly, in vivo and in vitro research reveals that sevoflurane may hinder the metastatic potential of lung cancer by limiting platelet activation better than other volatile agents. Still, sevoflurane can enhance different metastasis pathways at high doses by increasing MMP-9 expression more than propofol. Likewise, propofol also has anti-metastatic abilities, hindering angiogenesis by downregulation of necessary growth factors when combined with regional anesthesia. Clinical evidence supports a propofol TIVA for improved recurrence-free survivability, increased overall survivability, and decreased overall mortality more than inhalation anesthetics, regardless of the various tumor mechanisms affected by both anesthetics.

In conclusion, cancer recurrence and metastasis undoubtedly contribute to the low prognosis of patients after NSCLC resection surgery. Anesthetists may have the ability to improve long-term outcomes for their NSCLC surgical patients with the proper anesthetic. Propofol and sevoflurane are linked to some tumorigenic as well as antitumorigenic properties. Limited evidence reveals the correlation of propofol with better survival outcomes for patients

receiving cancer surgery, but the subjects were not entirely NSCLC patients. Ultimately, more

research is needed to justify one anesthetic over the other. In patients undergoing lung surgery, a

homogenous, large center RCT evaluating propofol and sevoflurane effects on recurrence-free

survival, overall survivability, and overall mortality would decisively provide anesthetists a

straightforward approach to saving more lives of NSCLC patients. RCTs with a balanced

anesthetic approach, including using both sevoflurane and propofol, may be beneficial.

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