Anesthesia, surgical stress, and “long-term” outcomes

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1. Introduction

An increasing body of evidence shows that the choice of anesthetic can strongly influence more than simply the quality of anesthesia. Regional and general anesthesia have often been compared to ascertain whether one provides benefits through dampening the stress response or harms by accelerating cancer progression. Regional anesthesia offers considerable advantages, by suppressing cortisol and catecholamine levels and reducing muscle breakdown postoperatively. It also has less immunosuppressive effect and potentially reduces the proinflammatory cytokine response. As such, vital organ functions (e.g., brain and kidney) may be better preserved with regional anesthetics, however, further study is needed. Volatile general anesthetics appear to promote cancer malignancy in comparison to regional and intravenous general anesthetics, and reduce the body’s ability to act against cancer cells by suppression of natural killer cell activity. There is not sufficient evidence to support an alteration of current clinical practice, however, further research into this area is warranted due to the potential implications elicited by current studies.

2. Surgical stress response

Surgical stress is a spectrum of changes occurring throughout different systems in the body (Figure 1). Raised adrenocorticotropic hormone (ACTH) induces excess cortisol release and leads to insulin resistance, raising blood glucose levels. This can have negative consequences, as hyperglycemia has been shown to increase wound infection postoperatively. Immunological changes also occur during surgical stress and there is an increase in leukocyte infiltration to the area of damage, as well as raised levels of dendritic cells within the circulation. Surgical stress has also been shown to have an immunosuppressive effect, reducing natural killer (NK) cell toxicity and T-cell responses.

The endocrine response has a large role to play within surgical stress. Epidural anesthesia in addition to GA has been shown to reduce the increase in cortisol and urinary epinephrine intraoperatively, when compared to GA alone. When comparing intravenous with volatile GA, it has been reported that propofol combined with remifentanil inhibits the ACTH–cortisol axis and catecholamine and growth hormone increase compared to volatile GA.

Metabolic changes secondary to surgical stress include an increase in proteolysis after surgery, leading to muscle breakdown and loss. The use of a combined spinal and epidural blockade...
Figure 1. Demonstration of the relationship between surgical trauma and the multi-system effects of the surgical stress response. These are dampened to a greater extent (indicated by a greater number of minus markers in the figure) by regional anesthesia in comparison to general anesthesia. NK – natural killer.

2.2. Surgical stress and other organs

A reduction in renal function secondary to surgical interference is a well-known effect. As previously mentioned, the use of opioids such as fentanyl leads to obtundation of the surgical stress response; Kono et al. compared the effects of halothane and fentanyl anesthesia on renal function during coronary artery surgery. They found that the use of fentanyl reduced the hormonal response, including a reduction in cortisol, vasopressin, and aldosterone. This led to improved creatinine clearance compared to halothane. They concluded that the reduction in hormonal response was likely responsible for the improved creatinine clearance, however, it is important to still take into consideration other factors. For example, halothane has also been shown to decrease endothelial-mediated vasorelaxation, and therefore, a comparative reduction in renal blood flow may also have contributed to a poorer creatinine clearance. An overview of the proinflammatory cytokines associated with the surgical stress-induced immune response, such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-alpha, has been shown within the hippocampus postoperatively and is associated with the development of POCD in murine models.

Studies looking at the effect of RA, compared to that of GA, on the rates of POCD present a mixed picture. Rasmussen et al. demonstrated no significant difference between RA and GA in rates of POCD; however, another study showed significantly poorer cognitive function in those patients undergoing GA than RA. Each study included patients undergoing noncardiac surgery, but both had biases such as large dropout rates and failure to account for social factors. As previously discussed, RA leads to a reduced stress response in comparison to GA. This suggests that although levels of surgical stress can be associated with POCD, its role as a causative factor is still uncertain. Promising results for the therapeutic treatment of POCD have been shown by Vizcaychipi et al., who pretreated mice using atorvastatin. Atorvastatin has previously been shown to protect against neuroinflammation, and demonstrated a significant reduction in cognitive decline postoperatively within their study.

Other negative sequelae of undergoing surgery, specifically under GA, have been demonstrated, although much of the work is still preclinical. For example, it has been shown that an elderly person undergoing GA is at a higher risk of developing dementia. This may be related to the fact that higher rates of brain atrophy have been detected within elderly patients who had undergone surgery, compared to those who had not. Tang et al. showed that surgery, independent of anesthesia, has the ability to propagate some of the pathological mechanisms behind Alzheimer’s disease. Using a murine model, they demonstrated an increase in amyloid-β plaque density, phosphorylation, and microglial activity. The inflammatory nature of the surgical stress response may be a contributing factor for this. Guo et al. showed that deposition of amyloid plaque is dependent on systemic inflammation in a murine model and also associated with increased levels of inflammatory cytokines in brain tissue. One of the initial regions to be affected by Alzheimer’s disease is the hippocampus, and the increase in IL-1β and IL-6 within the hippocampus after surgery could be a potential driving factor for its development. Because the systemic inflammatory response is intertwined with surgical stress, it is possible that down-regulation of the surgical stress response may show benefits in reducing the progression and rate of Alzheimer’s disease in elderly patients undergoing surgery. Current research (Table 1) is limited to murine models, and this is an area where future studies in humans may prove beneficial.

2.1. Surgical stress and the brain

The brain leads the surgical stress response by initiating changes in the neuroendocrine balance; however, it can also be negatively impacted by this alteration in homeostasis. A major consequence of this is postoperative cognitive dysfunction (POCD). This is a “deterioration in cognition temporally associated with surgery” and is associated with higher mortality three months postoperatively. It has been found that alterations in the endocrine response to surgery can influence the risk of developing POCD. Higher cortisol levels postoperatively have been shown to be associated with a higher chance of developing POCD along with suppression of the growth hormone axis. Increased presence of immune system effects of the surgical stress response. These are dampened to a greater extent (indicated by a greater number of minus markers in the figure) by regional anesthesia in comparison to general anesthesia. NK – natural killer.
literature comparing the effects of RA and GA on morbidity and mortality showed that the use of RA reduced the rates of renal failure. With regard to the gastrointestinal tract, a meta-analysis found that epidural anesthesia reduces the incidence of paralytic ileus after abdominal surgery. This may be due to the blocking effect of RA on the adrenergic response. Catecholamines have been shown to reduce gut motility, an effect that has also been demonstrated in animal studies to be potentiated by the opioid sufentanil. In cardiac surgery, thoracic epidural anesthesia, in comparison to GA, has been shown to reduce both supraventricular tachyarrhythmias and respiratory complications. To date, no studies have shown that this is linked to an improvement in mortality, once again presenting an area where longer-term studies may show a benefit.

3. Influence of anesthetic type on cancer outcomes and recurrence

Previous research indicates that the choice of anesthetic technique may have an effect on cancer progression by influencing cell invasion, migration, proliferation and metastasis. Clinical studies indicate that RA and/or intravenous GA can be preferable for cancer patients in comparison to volatile GA, with regard to outcomes. Breast cancer patients who underwent surgery with a paravertebral nerve block in combination with GA have a lower incidence of cancer recurrence or metastasis than those undergoing surgery with GA and patient-controlled morphine analgesia. Another study has shown that the recurrence rate of prostate cancer after prostatectomy under GA with epidural analgesia was significantly ameliorated this cognitive dysfunction (p < 0.05). POCD after 1 wk was greater after GA than after RA (19.7% vs. 18.3%). No significant difference was found in the incidence of cognitive dysfunction 3 mo after GA/RA. MMSE scores decreased after GA in comparison to RA (p = 0.0051). No statistical differences in other neuropsychological tests.
significantly lower than that under GA with postoperative opioid analgesia. In addition, patients with ovarian adenocarcinoma who underwent surgery with epidural anesthesia and analgesia had better long-term outcomes than those who were given only GA, and excision of melanoma under GA has been associated with a decreased survival rate when compared to patients who had excision under a local anesthetic. Furthermore, a retrospective study, reporting the data from 2838 patients registered for surgery for breast, colon, or rectal cancer, showed that propofol anesthesia might be better than sevoflurane in surgery for cancer types for 1-year survival, however, after adjustment for several confounders, the observed differences were not statistically significant. These studies are summarized in Table 2.

### 3.1. Effect of anesthetic choice on anticancer immunity

Cell-mediated immunity with T-helper 1 (Th1) cells and NK cells is considered an important mechanism in enabling the body to act against cancer. It has been associated with reduced risk of cancer recurrence after surgical resection, because NK cells are reported to have cytolytic activity against cancer cells. Volatile GA has been shown to suppress this anticancer immunity. It has also been reported that NK cells target cancer cells and prevent metastases, which is supported by evidence showing a correlation between higher recurrence rates and reduced NK cell activity. NK cell cytotoxicity is decreased by all types of anesthesia, but GA in particular appears to have a greater effect. Ketamine, thiopental, and halothane reduced NK cell activity and increased tumor retention and metastasis. Propofol has been shown to have protective effects through a variety of mechanisms that enhance antitumor immunity. A possible reason for this is that intravenous GA, when compared to volatile GA has been shown to increase IL-10, which is known to have antitumor activity and help with healing and repair.

Epidural anesthesia in combination with GA, compared to GA alone, has been shown to increase the ratio of Th1 cells to Th2 cells in patients with hepatocellular carcinoma, potentially promoting antitumor activity. The Th1/Th2 ratio has also been shown to decrease after volatile GA, whereas propofol did not induce any change. These findings show that volatile GA is more likely to suppress anticancer immunity to a greater extent than intravenous GA or RA.

### 3.2. Effects on "oncogenes," matrix metalloproteinase, and hypoxia inducible factors

Volatile GA has been shown to modulate gene expression in breast and brain tumor cell cultures, occurring in a unique and time-dependent manner. Compared with volatile GA, intravenous GA with RA reduces postoperative IL-1β, suppresses elevation of matrix metalloproteinase (MMP)-3 and MMP-9, and also reduces the increase in hypoxia inducible factor (HIF)-1α and HIF-2α. MMPs are known to be involved in cancer cell invasion, migration, and metastasis. HIF-1α overexpression is associated with poor survival rates and a reduced disease-free rate in colorectal cancer. It has also been shown to reduce response to therapy and shorten disease-free survival in breast cancer patients. Volatile GA has been shown to upregulate HIF-1α expression and enhance cancer malignancy. Recent studies have demonstrated that isoflurane upregulates HIF-1α in prostate cancer cells, but propofol downregulates these increases. Both HIF-1α and HIF-2α were upregulated by isoflurane in renal cancer cells as well. Other inhalational anesthetics also upregulate the HIF system, and the possible link to cancer malignancy has been discussed previously. In addition to this, barbiturates have been shown to inhibit HIF-1α activation, whereas local anesthetics used in RA reduced HIF-1α expression. These studies indicate that volatile GA enhances cancer invasion and metastasis to a greater extent than intravenous GA or RA. However, further research, including large clinical trials, are

**Table 2: Anesthesia versus cancer.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Species/model</th>
<th>Anesthetic/pharmacological agents</th>
<th>Protocol</th>
<th>Major findings</th>
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<tbody>
<tr>
<td>Exadaktylos et al</td>
<td>Anesthesiology Retrospective study Single center</td>
<td>Paravertebral anesthesia (Th2/3, 0.25% Bupi 0.2 ml/kg GA [fentanyl 0.5 μg/kg, propofol 1.5–3.0 mg/kg, Sevo [2–3%] + paravertebral anesthesia (Th2/3, 0.25% Bupi 0.2 ml/kg GA + postoperative morphine (0.05 mg/kg, i.v.)</td>
<td>Mastectomy and axillary clearance for breast cancer Kaplan–Meier method</td>
<td>The paravertebral group had slower time to recurrence (p = 0.013) in 1-y follow up. No significant differences in patients or surgical details, tumor presentation, or prognostic factors</td>
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<tr>
<td>Lin et al</td>
<td>BJA Retrospective study Single center</td>
<td>Epi: Epidural (MDZ 0.04 mg/kg, Th11/12 or 12/3, Bupi 0.125% or Ropi 0.150%) + analgesia (morphine 0–8 mg) GA: GA (MDZ 0.04 mg/kg, fentanyl 3–4 μg/kg, propofol 1–2 mg/kg, Vb 0.1 mg/kg, Sevo 2–3%, or Is 1.5–2.5%) + postoperative i.v. fentanyl</td>
<td>Surgery for ovarian serous adenocarcinoma Cox proportional hazards analysis</td>
<td>Epi reduced mortality compared to GA during the initial years of follow up (hazard ratio 1.214, p = 0.043)</td>
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<tr>
<td>Schlagenhauff et al</td>
<td>Melanoma Res Retrospective study Single center</td>
<td>Not available</td>
<td>GA: propofol ± epidural GA: Sevo + N2O ± epidural Doses not mentioned</td>
<td>Surgery for primary melanoma Cox proportional hazards analysis</td>
<td>GA decreased the survival rate compared to RA (relative risk 1.46, p &lt; 0.0001) Overall 1- and 5-y survival rates of propofol are better than sevoflurane anesthesia. No significant differences in the 1-y survival for patients operated for colon cancer after adjustment</td>
</tr>
<tr>
<td>Enlund et al</td>
<td>Ups J Med Sci Retrospective study Single center</td>
<td>Not available</td>
<td>GA: propofol ± epidural GA: Sevo + N2O ± epidural Doses not mentioned</td>
<td>Surgery for breast, colon, or rectal cancers Kaplan–Meier method Cox proportional hazard analysis</td>
<td>GA decreased the survival rate compared to RA (relative risk 1.46, p &lt; 0.0001) Overall 1- and 5-y survival rates of propofol are better than sevoflurane anesthesia. No significant differences in the 1-y survival for patients operated for colon cancer after adjustment</td>
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needed prior to concluding that specific anesthetics and techniques influence cancer recurrence postoperatively.

4. Conclusion

It is difficult to perform a conclusive comparison between GA and RA due to the huge variety of anesthetic techniques available, as well as the varying anesthetic demands in surgery for a wide range of issues, including malignancy. The current literature looks at specific scenarios and is significantly limited by the lack of applicability to a wider context.

There is a strong argument supporting the wider and preferential use of RA and intravenous GA compared to volatile GA in circumstances where possible. These might include patients diagnosed or potentially malignant tumors, or those particularly vulnerable to the surgical stress response. Sufficient evidence to support an immediate alteration of current clinical practice is lacking; however, further research into this area is warranted due to the potential implications elicited by the current research.

References


