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Review Article

# Anesthesia, surgical stress, and "long-term" outcomes

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ABSTRACT

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.



## 1. Introduction

An increasing body of evidence shows that the choice of anesthetic can strongly influence more than just the quality of anesthesia. The body's stress response to surgery first became a subject of interest in the 1920s, when David Cuthbertson[1] observed that surgical patients had a large increase in urinary muscle breakdown metabolites postoperatively. Since then, studies have looked into detailing the stress response and whether it can be altered to the patient's advantage. Anesthetic choices can also have much wider implications, affecting cancer cell biology and its progression toward metastasis and invasion. This review will be looking specifically at the effects of regional anesthesia (RA) compared to general anesthesia (GA) with intravenous and volatile reagents, and the impacts of both of them on altering the surgical stress response, postoperative organ function and cancer progression.

## 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.[2] Immunological changes also occur during surgical stress and there is an increase in leukocyte infiltration to the area of damage,[3] as well as raised levels of dendritic cells within the circulation.[4] Surgical stress has also been shown to have an immunosuppressive effect, reducing natural killer (NK) cell toxicity and T-cell responses.[5]

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.[6] 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.[7]

Metabolic changes secondary to surgical stress include an increase in proteolysis after surgery, leading to muscle breakdown and loss.[8] The use of a combined spinal and epidural blockade

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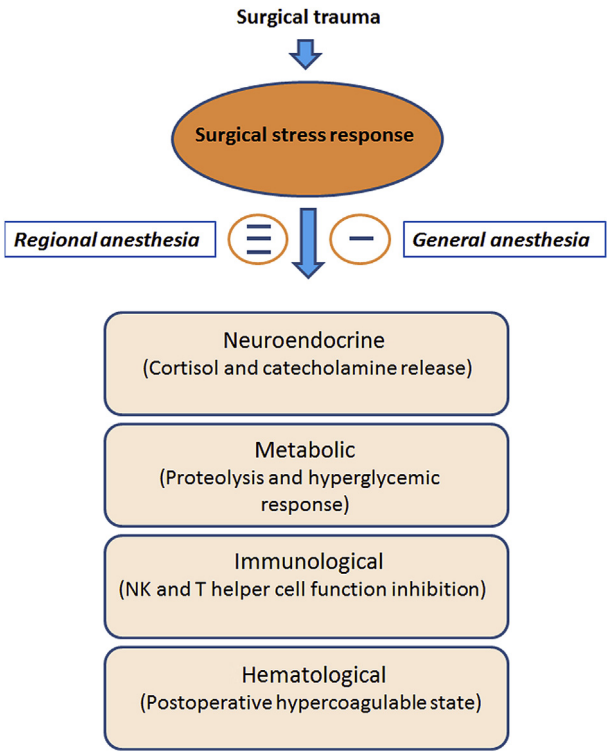


**Figure 1.** Demonstration of the relationship between surgical trauma and the multisystem effects of the surgical stress response. These are dampened to a greater extent (indicated by a greater number of minus markers in the figure) by regional anesthesia in comparison to general anesthesia. NK = natural killer.

during hip surgery has been shown to attenuate the increase in amino acid oxidation 24 hours after surgery, in comparison to GA.[9] Among GA reagents, the use of propofol has been found to cause a reduction in the proteolytic response to surgery, by potentially allowing the body to make use of triglycerides contained within the propofol emulsion as a substitute.[10] The increase in glucose production during surgery can also be prevented by epidural analgesia, yet inhaled anesthetics appear to have no effect.[11]

The effects of volatile and intravenous general anesthetics on the immune system have also been shown to differ. Ketamine, thiopental and halothane have all been reported to suppress the activity of NK cells; however, propofol has been reported to increase interferon gamma release from NK cells.[12,13] It has also been shown that volatile and intravenous GA have a variety of effects on cytokines depending on the anesthetic agent used.[14,15] Lastly, volatile GA impairs platelet aggregation and clot stability in comparison to propofol.[16]

### 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"[17] and is associated with higher mortality three months postoperatively.[18] 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,[19] along with suppression of the growth hormone axis.[20] Increased presence of proinflammatory cytokines associated with the surgical stress-induced immune response, such as interleukin (IL)-6, IL-1β,[21] and tumor necrosis factor-alpha,[22] 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[23] 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.[24] 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,[25] 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.[26] 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.[27] Tang et al[28] 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, τ phosphorylation, and microglial activity. The inflammatory nature of the surgical stress response may be a contributing factor for this. Guo et al[29] 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,[30] and the increase in IL-1β and IL-6 within the hippocampus after surgery[31] could be a potential driving factor for its development. Because the systemic inflammatory response is intertwined with surgical stress,[32] it is possible that downregulation 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.[33]

### 2.2. Surgical stress and other organs

A reduction in renal function secondary to surgical interference is a well-known effect.[34] As previously mentioned, the use of opioids such as fentanyl leads to obtundation of the surgical stress response; Kono et al[35] 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,[36] and therefore, a comparative reduction in renal blood flow may also have contributed to a poorer creatinine clearance. An overview of the