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The Evaluation of the Influence Increased Immunomodulatory Effects of Anesthetic Drugs in Elderly Patients in the Perioperative Phase: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Every drug, taken for whatever purpose, has its set of implications on the patient. These drugs, apart from causing the desired effects in an individual's body, also work to cause several interactions with different parts of the body. In doing so, they may alter several mechanisms and also cause side effects if taken suddenly or without any checks and balances. These side effects are problematic and also the reason that causes a patient's body to malfunction in the long run. In a very similar way, the impact of increased immunomodulatory effects of anesthetic drugs in elderly patients during the perioperative phase is an important topic in the field of anesthesiology and perioperative medicine. It is a well-known fact that anesthetic drugs, particularly intravenous anesthetics like propofol and inhalational anesthetics like isoflurane, can have immunomodulatory effects. These drugs can influence the immune response of the body, including cytokine

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production, leukocyte function, and the inflammatory response. However, the target audience here, that is, the elderly population is often already experiencing age-related changes in their immune system, a condition referred to as immunosenescence. This can lead to a less robust immune response, making them more susceptible to infections and complications. However, the pre-operative phase is a critical period when the patient's body is exposed to various stressors, including surgery itself, tissue damage, and potential infections. This phase is when the immune system plays a significant role in maintaining the patient's health. During such a delicate phase, anesthetic drugs may make elderly patients more vulnerable to postoperative infections. This can lead to longer hospital stays, increased healthcare costs, and a higher risk of complications. Immune suppression can also result in delayed wound healing and a slower recovery process. This can affect the overall quality of life for elderly patients. To address these problems, this review has been designed with the intention of highlighting all such problems that arise with the usage of anesthetic drugs in elderly patients.

Keywords: Anesthetic drugs; propofol; immunomodulatory effects; elderly patients; side effects of anesthesia.

1. INTRODUCTION

The primary objectives of general anesthesia mainly include the induction of amnesia, unconsciousness also referred to as hypnosis, and the immobilization of the patient.

It is a fundamental goal or milestone that general anesthetics are intended to achieve these three essential therapeutic effects in a reversible manner. These therapeutic goals are accomplished through the administration of general anesthetic drugs, which may be administered via inhalation or intravenous routes. Furthermore, anesthesiologists may employ other classes of pharmaceutical agents to address specific clinical objectives in the perioperative setting [1].

Within this broad-spectrum approach, anesthetists frequently employ drugs that selectively impede neuromuscular transmission, thereby mitigating patient movement and optimizing the conduct of surgical procedures [2].

Additionally, benzodiazepines find application in the anesthetic protocol to instill anxiolysis and evoke anterograde amnesia, while opioids play a crucial role in delivering analgesia - an action characteristically exhibited by only a limited subset of general anesthetics [3].

It is imperative to underscore that, among the wide variety of pharmaceutical agents that are actively employed by anesthetists, general anesthetics stand as unique agents, singularly designated to induce the state of unconsciousness in patients throughout the perioperative phase [4].

In the recent decade, the development of several novel sedative and anesthetic drugs has been garnered necessary by evolving clinical demands. Procedures confined to hospital settings are now routinely conducted in outpatient environments. Concurrently, the goal to contain healthcare costs has elevated the demand for intravenous agents characterized by ease of administration, even by non-specialist healthcare practitioners, and devoid of the costly equipment requirements associated with inhaled anesthetics [5].

The ideal candidates among these agents would possess the capacity to provide anesthesia or sedation in a rapidly titratable manner, marked by swift onset and recovery. Moreover, they would be distinguished by minimal side effects, including respiratory and cardiovascular depression, nausea, vomiting, and injection site pain. Ultimately, the perfect anesthetic agent would boast a high therapeutic index and lend itself to straightforward formulation in an aqueous solution. As of the present moment, no hypnotic agent with all these coveted attributes is available in clinical practice [6].

Among the sedative-hypnotic agents commonly employed by anesthesiologists, midazolam, and propofol occupy a prominent position. These two agents, midazolam and propofol, are often used to induce sedation and anesthesia, respectively. Nevertheless, when administered at appropriate doses, both midazolam and propofol are capable of achieving either clinical endpoint [7]. Their mechanism of action involves the potentiation of inhibitory actions at GABA receptors in the central nervous system. This possess allows for

the channel opening and facilitating the diffusion of chloride ions into neuronal cells. This results in hyperpolarization, thereby diminishing the neuronal cell's capacity to initiate an action potential, ultimately leading to central nervous system depression [8].

2. THE IMPACT OF IMMUNOMODULATORY ANESTHETIC DRUGS ON ELDERLY PATIENTS

Immunosenescence combined with the immunomodulatory effects of anesthetic drugs can increase the risk of various complications, such as pneumonia, surgical site infections, and sepsis. It is for reasons like these that it is important to note that the response to anesthetic drugs and their immunomodulatory effects can vary among individuals. Some elderly patients may be more affected than others [9].

Throughout the span of surgical procedures being performed, given here is an overview of some of those conditions in which anesthetic drugs indeed have an impact on the lives of elderly patients.

2.1 Transplantation Surgery

A significant amount of research work has been devoted to devising strategies aimed at mitigating ischemia-reperfusion (I/R) injury.

This condition arises as transplanted organs undergo a series of ischemic insults, from the initial injury sustained by the donor organ to the subsequent surgery on the recipient. The ischemia-reperfusion (I/R) injury can manifest even in a sterile environment, and its effects have a striking resemblance to the activation of the host's immune response against invading pathogens [10].

This sterile immune response hinges on a cascade of signaling events mediated by pattern recognition molecules, with Toll-like receptors at the forefront, and it also involves the recruitment and activation of immune cells, both from the innate and adaptive systems. During the critical early phases of reperfusion, innate immune cells play a pivotal role in either driving pathological inflammation, collateral tissue damage, or conversely, facilitating the resolution of injury [11].

Researchers have explored two primary categories of interventions to shield against ischemia-reperfusion (I/R) injury. The first is ischemic preconditioning (IP), which involves exposing the tissue to a brief ischemic insult prior to a more prolonged ischemic episode [12].

The second category centers on pharmacological preconditioning, with a focus on volatile anesthetics (VA). These volatile anesthetics have exhibited organ-protective properties, as evidenced in cardiac surgery and liver resection, primarily attributed to their ability to release antiapoptotic factors [13].

Ischemia-reperfusion (I/R) injury is associated with a range of detrimental effects, including the adhesion of neutrophils and platelets to the vessel walls, the deterioration of the endothelial glycocalyx, dysfunction of the endothelium and microvasculature, proinflammatory activation, and oxidative stress [14].

Notably, anesthetic agents play a role in attenuating the inflammatory response, and their actions are modulated by nitric oxide (NO) as well as the activity of inducible nitric oxide synthase (iNOS). Furthermore, these agents impede intercellular communications, particularly at gap junctions, thereby ameliorating the damage induced by I/R. Remarkably, volatile anesthetics have demonstrated their capacity to protect tissues from I/R injury when administered prior to the induction of ischemia [15].

This approach has shown promise in enhancing metabolic and organ function, spanning the heart, lungs, kidneys, and brain.

2.2 Neurocognitive Functioning

The aging process exerts a multifaceted influence on both the pharmacokinetics and pharmacodynamics of anesthetic agents. This is because it constitutes an independent risk factor for postoperative cognitive dysfunction (POCD).

In the geriatric population, the administration of benzodiazepines warrants particular caution, as they can elicit excessive sedation, necessitating their prescription in low doses.

Propofol, given its rapid metabolism, emerges as a suitable choice for patients with neurodegenerative diseases; however, its use may not be advisable in individuals with Parkinson's disease due to its potential to induce spontaneous involuntary movements [16].

The administration of inhaled anesthetics in older adults should be approached judiciously, bearing in mind the risk of respiratory and cardiovascular depression.

Notably, regional anesthesia may offer advantages for patients with Parkinson's disease, affording them the opportunity to continue taking oral levodopa both preoperatively and throughout the surgical and postoperative phases [17].

2.3 Growth of Cancer

Because of the link between surgical stress responses and the potential immunosuppressive effects of anesthetic agents, concerns have arisen regarding an elevated risk of metastatic spread.

The association of immune responses is under the influence of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), both of which can be activated by surgery or anesthesia and potentially foster metastasis through the release of soluble factors from tumors.

When activated, these factors serve to dampen cell-mediated immunity, culminating in the liberation of prostaglandin E2 and catecholamines. These, in turn, usher in an environment rife with immunosuppressive and pro-inflammatory cytokines, notably interleukin-6 (IL-6) and interleukin-8 (IL-8), which actively contribute to tumor angiogenesis and metastatic progression.

Preclinical studies have offered valuable insights into the distinct impacts of various agents used in anesthesia on cancer cells [18].

The effects are contingent upon factors such as dosage, duration, and timing. For instance, sevoflurane has demonstrated the capacity to suppress hypoxia-induced growth and metastasis in lung cancer cells, while isoflurane, conversely, appears to heighten the malignant potential of ovarian cancer cells. In experimental settings, morphine at clinically relevant doses has been shown to promote tumor neovascularization, angiogenesis, and tumor progression [19].

On the other hand, regional anesthesia and the use of propofol appear to reduce the perioperative stress response. In clinical practice, however, there is a dearth of substantial evidence to conclusively assert that anesthetic choices influence cancer outcomes. Thus, the imperative for prospective clinical trials to comprehensively assess the effects of anesthetics on cancer recurrence after surgery is evident.

2.4 Obesity

When referring to obese patients, the choice of anesthetic drugs necessitates careful consideration, given the distinct alterations in pharmacokinetics, the presence of comorbidities, and the likelihood of concurrent sleep-disordered breathing.

Obesity often accompanies chronic low-grade inflammation, and anesthesia plays a pivotal role in modulating the disrupted immune function associated with this condition [20].

Notably, volatile anesthetics have been safely employed for maintaining general anesthesia in obese patients. In the postoperative phase, agents like dexmedetomidine and clonidine are valued for their minimal respiratory depressant properties, contributing to improved patient outcomes.

Moreover, the adoption of multimodal analgesia techniques, inclusive of local anesthesia, holds the potential to reduce opioid usage, ultimately enhancing the postoperative recovery of obese patients. In terms of immune function, the need for randomized clinical studies becomes evident, as they can provide a comprehensive understanding of the immunomodulatory properties inherent in anesthetic agents when administered to this specific patient population.

A noteworthy development in this area is the design of a pilot protocol randomized trial, which aims to compare the effects of two commonly used anesthetic agents, sevoflurane and propofol, on circulating levels of inflammatory biomarkers and the differentiation of adipose tissue macrophages in obese patients undergoing bariatric laparoscopic surgery.

The outcomes of this trial promise to furnish valuable evidence concerning the potential immune effects of these widely employed anesthetics within the context of obesity, thereby enriching our understanding of this critical aspect of perioperative care in this patient demographic.

3. OVERVIEW OF THE IMMUNOMODULATORY EFFECTS OF DIFFERENT ANESTHETIC AGENTS

Here is an overview regarding the insights into the diverse effects of anesthetic agents on immune function, emphasizing their potential to modulate various facets of the immune response in clinical and experimental settings.

3.1 Volatile Anesthetics

3.1.1 Sevoflurane

It demonstrates a capacity to reduce several immune parameters, such as diminishing polymorphonuclear neutrophils (PMNs), reactive oxygen species (ROS) levels, chemotaxis, and pro-inflammatory cytokines [21].

3.1.2 Desflurane

It has been associated with genotoxic and pro-inflammatory effects, especially in the context of minor surgical procedures [22].

3.2 Intravenous Anesthetics

3.2.1 Dexmedetomidine

It exhibits anti-inflammatory properties by decreasing pro-inflammatory cytokine levels in experimental sepsis. It also reduces neutrophil infiltration and prevents lung injury [23].

3.2.2 Ketamine

It shows a reduction in levels of pro-inflammatory cytokines, decreases nitric oxide (NO) production by macrophages (Mφ), and modulates natural killer (NK) cell functioning.

It enhances the Th1/Th2 ratio and overall immune function, while also reducing neutrophil adhesion, degranulation, and antioxidant activity [24].

3.2.3 Propofol

It negatively affects Mφ chemotaxis, oxidative burst, and phagocytosis, and decreases inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokine levels [25].

It has also been associated with a decrease in pulmonary immune response and exhibits antiapoptotic and neuroprotective effects. Propofol reduces neutrophil superoxide and elastase release, as well as chemotaxis while inhibiting platelet aggregation.

3.2.4 Barbiturates

They show anti-inflammatory effects, including suppression of neutrophil antibacterial functions, reduced neutrophil polarization, chemotaxis, adherence, phagocytosis, and oxidative burst, along with a decrease in pro-inflammatory cytokines. They also exhibit protective effects against T-lymphocyte apoptosis [26].

3.2.5 Benzodiazepines

They have diverse effects, including the suppression of neutrophil function and the activation of mast cells, reduction in pro-inflammatory cytokine levels, and promotion of the M2 monocyte/macrophage phenotype [27].

3.2.6 Opioids

They have a wide range of impacts, such as a decrease in macrophage (Mφ) counts at the site of infection, reduced Mφ phagocytosis, and attenuation of the bactericidal function of neutrophils.

They also influence T-cell responses, affecting antigen presentation, the early pro-inflammatory response to opportunistic infections, and altering differentiation to a Th2 phenotype [28].

3.3 Local Anesthetics

These agents exhibit anti-inflammatory effects by impacting polymorphonuclear neutrophils (PMN) and macrophages (Mφ). They reduce adherence, migration, and accumulation at the site of inflammation, and edema formation, and help preserve endothelial barrier integrity [29].

4. CONCLUSION

Contemporary advances in molecular pharmacology and the study of transgenic animal models are progressively unveiling a different narrative. These innovations are shedding light on the properties of certain general anesthetics, revealing that they exhibit a degree of selectivity. In particular, they target essential CNS structures and specific molecular pathways that play a pivotal role in the modulation of the intricate processes associated with consciousness. In conclusion, the increased immunomodulatory

effects of anesthetic drugs in elderly patients during the perioperative phase can have important clinical implications. Anesthesiologists and healthcare teams should carefully consider these effects when planning and managing the care of elderly surgical patients to minimize the risk of complications and promote a smooth recovery.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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