Journal of Positive Psychology & Wellbeing http://journalppw.com
2022, Vol. 6, No. 3, 363 – 375 ISSN 2587-0130

Effect of General Anesthesia on Postoperative Cognitive Function in Elderly Patients

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Abstract

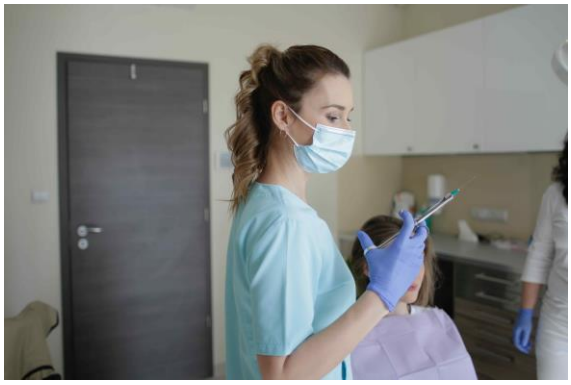
The prevalence of postoperative cognitive dysfunction continues to be significant following surgical procedures. It has been posited that external factors, among which the type of anesthesia plays a vital role, are significant contributors to POCD. In older adults, cognitive decline post-surgery can lead to devastating physical, psychological, and societal impacts. Advancing our comprehension of cognitive deterioration postoperatively is critical for eradicating this potentially avoidable contributor to cognitive decline. Therefore, a thorough grasp of the cognitive repercussions of various anesthetic agents used intraoperatively has become crucial. This surge of interest has propelled research focusing on the repercussions of general anesthesia on post-surgical cognitive abilities. The objective of this literature review is to enrich readers' insights into POCD among the geriatric demographic and to scrutinize the evidence of how various anesthetic components—mainstay anesthetics, supplemental agents, and sedatives—influence postoperative cognition. Prior to the 1950s assumptions, it was surmised that anesthesia merely rendered cerebral functions dormant during surgery, with normalcy resuming upon awakening. Contemporary understanding now acknowledges the nuanced impact of anesthetics, which instigate distinctive alterations in specific cerebral activities and memory capacities. Concerns about post-surgical cognitive deficit burgeoned with the advent of inhalational anesthetic pharmacology, paralleled by heightened life expectancy and health service utilization in the aging population. While minor surgical interventions like dental extractions, often under local anesthesia, were thought to yield better cognitive outcomes, this notion was upended by Bedford's revelation in 1960 that major surgical procedures such as coronary bypass, involving cardiopulmonary bypass and extended hypothermia, markedly disrupted cognitive faculties. This link between significant surgical interventions and cognitive impairment fueled further inquiry into the influence of surgery and anesthetic agents on postoperative brain function. The late 1970s witnessed heightened awareness of postoperative "forgetfulness" in the aged, evolving into substantial focus in the late 1990s. At that point, profound documentation surfaced indicating cognitive decline post-surgery was pervasive across all ages but was especially pronounced in elderly individuals—representing a critical public health concern. The era following this revelation has witnessed an avalanche of studies probing into POCD.

Keywords*: postoperative cognitive dysfunction, anesthesia.*

1. Introduction

Study Objective: Our investigation focuses on scrutinizing the repercussions of general anesthesia on postoperative cognitive abilities in the senior population. Through a systematic review combined with a meta-analysis, we plan to dissect the following query: Does general anesthesia precipitate an elevated occurrence of postoperative cognitive dysfunction (POCD) in older individuals facing elective surgeries in contrast to those who forgo such anesthesia? Our findings aim to lay down recommendations for geriatric surgical candidates and substantiate the advantages of opting for regional anesthesia when possible.

Context: A surge in the elderly demographic coupled with prolonged longevity foretells a sharp rise in the geriatric surgical community. As we witness our society age, grasping the extent of postoperative consequences for this group becomes increasingly crucial, including risks uniquely pertinent to older patients undergoing general surgery. POCD stands out as a frequent surgical aftermath, notably in the aging population. Elusively defined, POCD's diagnosis challenges physicians, especially when determining the appropriate cognitive baseline deviation post-procedure. Commonly, the condition is identified through a decrease in mental acuity within one week or one month post-operation. Others regard the emergence of new cognitive deficits following surgery as indicative of POCD. A considerable span of patients, varying from 25% at hospital discharge to 10% after three months, find themselves affected. Notably, the incidence of POCD fluctuates across various surgeries—31% in cardiac operations and 12.7% in orthopedic interventions. POCD's implications extend to hospital stays, inflating costs notably, thereby exacerbating the financial strain on increasingly limited hospital resources. The resulting impact is a tarnished postoperative experience for the elderly. (Xiao et al., 2020)



1.1. Background

While avoiding surgical interventions through alternative therapies or lifestyle adaptations may serve as the optimal strategy against cognitive deterioration, it's imperative to evaluate anesthesia and surgical-specific factors. These elements encompass anesthetic selection, efforts to circumvent intraoperative hypotension, and the application of less invasive operative methods. With rising numbers of post-surgical elderly patients, and the profound impact of cognitive decline upon life quality and healthcare expenses, delving into this issue and potential interventions is of great importance. An ideal examination would engage in monitoring perioperative cognitive shifts in a broad, elderly cohort across varying surgical treatments. Cognitive evaluations before and after a surgical intervention, accounting for the standard mental decline linked to aging, as well as assessing inflammation and oxidative stress—presumed mechanisms behind the cognitive effects induced by anesthesia—would all feature in such a study. While numerous factors and health conditions heighten POCD risk, including inflammatory diseases, anemia, and advanced age, general anesthesia surfaces as a notably alterable factor contributing to cognitive regression. The pathway through which anesthesia leads to POCD is yet to be unraveled entirely. Nevertheless, studies within animal models indicate that anesthetics like isoflurane and midazolam could potentiate beta-amyloid protein oligomers, indicative of Alzheimer's pathology. The administration of anesthesia, either prior to or following surgery with these agents, is known to impair cognitive functions postoperatively. Clinicians have long

acknowledged the occurrence of POCD, defining it as a decline in intellectual capacities amongst elderly post-surgical patients. Presented as memory, learning, concentration, and psychomotor pace deficits, POCD touches upon upwards of 52% of geriatric patients immediately after surgery, contingent on its definition and diagnostic evaluations utilized. Persistence of such impairments ranges from days to months for 25% of individuals and spans 3–6 months in 12%. This considerable morbidity source elevates the risk of premature retirement and the loss of autonomous living capabilities. Even fleeting bouts of cognitive disruption in the aged have been linked to heightened mortality rates following non-cardiac procedures. Increasing age predicates an individual's susceptibility to neurodegenerative disorders, Alzheimer's being the most prevalent, currently affecting 4.5 million American citizens. The disorder's frequency escalates with age and is set to triple over 50 years, leaping from 4.5 million to over 13 million individuals—an upsurge accompanied by profound fiscal and societal repercussions. This rise mirrors the anticipated growth in surgical necessities among the elderly, dealing with conditions like hip fractures, spinal stenosis, and peripheral vascular ailments. (Liu et al., 2022)

1.2. Purpose of the Study

An expanded exploration of objectives and a comprehensive methodological description are available in an accompanying piece in this issue of Anesthesiology and are thus not reiterated here. The specific objectives were as follows: (1) To ascertain if there is a discernible dip in cognitive prowess and a swell in POCD cases within the initial three postoperative days in seniors subjected to general rather than regional anesthesia. (2) To identify patient characteristics at baseline that may predispose them to an elevated risk of POCD subsequent to surgeries on lower extremities. (3) To investigate if an associational link exists between anesthetic treatment and a plunge in cognitive function or POCD prevalence, after balancing out demographic and the patient's medical profile. (4) To validate the hypothesis that general anesthesia stands as a POCD risk agent after orthopedic surgery by contrasting cognitive function in a cohort undergoing general anesthesia against a cognitively assessed and matched control group not subjected to surgery. The current study's mission was to deduce if general anesthesia notably raises POCD risks in elders undergoing orthopedic surgeries in comparison to regional anesthesia. This article sketches out the hypotheses, defined aims, and methodologies underpinning this inquiry. Postulated was the negative impact of lower extremity orthopedic surgeries on cognitive functions at hospital release, and the proposition that general anesthesia recipients witness a greater cognitive decline and bolstered POCD incidences within the first trio of postoperative days relative to patients administered regional anesthesia.

2. General Anesthesia and Cognitive Function

The effects of general anesthesia on cognitive abilities are multifarious, with a special emphasis on postoperative cognitive dysfunction (POCD). A wide variance in cognitive baselines among otherwise healthy aged individuals amplifies this risk. Since the mid-20th century, research has chronicled numerous instances of cognitive deficits following surgery, often presenting as a general cognitive malaise, memory complications, or severe stupor. General anesthesia's mechanism for inducing insensibility during surgical procedures notably includes cardiovascular implications, influencing heart rate and blood pressure among others. Given the rising prevalence of surgery among older demographics, the potential perioperative contributory factors to POCD have garnered significant investigation. Daily, statistics illuminate a commonality of cognitive complaints from seniors, implicating general anesthesia's role in potentially transient cerebral alterations. Anesthesia has been implicated not only in transient behavioral changes but also in increasing the odds for long-term cognitive conditions such as dementia and Alzheimer's disease. (Li et al., 2021)

2.1. Definition of General Anesthesia

Described as a medically-induced coma, general anesthesia is characterized by induced unconsciousness, analgesia, amnesia, and suppressed reflexes through inhalational or intravenous agents. The hallmarks of this state include a reversible insensitivity to stimuli, accompanied by unconsciousness that isn't disrupted even by painful interference. In addition to memory and pain suppression, the influence of anesthetic agents extends to perception, emotion, and cognitive faculties. Despite widespread application, the precise workings and target sites of anesthetics remain elusive. Evidence indicates heightened sensitivity of the reticular activating system, critical for consciousness, to these drugs. Substantive concern centers around the impairment of cognitive function, which incorporates mental acuity, information processing, memory, and problem-solving. While it's established that anesthetics dampen cognitive performance, their exact mechanisms remain unclear. This ambiguity perpetuates research into postoperative cognitive dysfunction (POCD), a condition marking a decline from baseline cognitive levels after surgery, particularly troubling in elderly patients where the risk of prolonged cognitive impairment is significant.

2.2. Impact of General Anesthesia on Cognitive Function

Senior individuals uniquely face the peril of POCD, aggravated by their diminished physiological capacity. Frequently, these individuals already exhibit some level of cognitive impairment, which is prone to exacerbation by surgical procedures and anesthesia. Evidence suggests that up to a quarter of dementia cases may arise post-surgery, with a portion attributably linked to anesthesia. Recovery of preoperative cognitive function can span up to three months in the elderly as opposed to a swifter recuperation in younger patients. This reveals the pronounced and enduring impacts of anesthesia on cognition in older adults. The severity and persistence of POCD also correlate with the type of surgery; more invasive procedures tend to exert greater psychological and physical stress. Through close monitoring, it has been noted that even moderate surgical trauma from orthopedic operations can significantly diminish cognitive abilities shortly after surgery. Thus, the patient's surgical experience, including potential complications, could further complicate the recovery of cognitive function.

2.3. Factors Influencing the Effect of General Anesthesia on Cognitive Function

Educational attainment levels are significantly correlated with the impact of anesthetic exposure on cognitive decline. Higher education levels and undergoing less intrusive surgical procedures seem to act as safeguarding factors against cognitive impairment post-anesthesia. Current knowledge does not ascertain whether removal from anesthetic agents would reverse cognitive alterations or prevent long-term cognitive aging. It is imperative from a health perspective to address cognitive effects when conducting future investigations into anesthetic practices. In light of our aging society and the consequent rise in elderly patients, even slight cognitive detriments linked to anesthesia could have extensive repercussions on memory loss. Presently, research methodologies have been restricted to examining acute mental status alterations. The necessity for broader neuropsychological evaluations and studies aimed at identifying subtler expressions of cognitive dysfunction is paramount.

3. Postoperative Cognitive Dysfunction (POCD)

Postoperative Cognitive Dysfunction, or POCD, manifests as a deterioration in cognitive abilities such as memory retention, the speed of cognitive processing, and the ability to flexibly shift thoughts, following surgical procedures. Diagnosis of POCD benefits from distinguishing between two types: overt cognitive dysfunction, which is observable to clinicians, and covert cognitive dysfunction, identifiable to the patient or close acquaintances but not openly evident. Different mechanisms and risk factors likely underpin

these two manifestations of POCD. Overt POCD diagnosis typically employs pre- and postoperative neuropsychological evaluations that encompass a broad spectrum of cognitive capacities, offering precise detection of cognitive decline.

3.1. Definition of POCD

Postoperative cognitive dysfunction, or POCD, signifies a significant post-surgical shift in cognitive performance, marking a downturn from a patient's standard cognitive abilities, impacting daily living activities and persisting over time. Emerging from an international working group's discourse, the definition of POCD hinges on data-driven considerations. Mental functions such as consciousness, awareness, perception, thought, reasoning, and recall fall under cognitive function, which can be evaluated through various means. Recognizing that different studies might employ differing assessments, the working party notes that tests can range from comprehensive neuropsychological to simple clinical examinations. Distinction from postoperative delirium and dementia is critical. POCD implies a gradual cognitive decline rather than the abrupt onset characteristic of delirium. Those with prior cognitive deterioration are particularly vulnerable to POCD, perhaps due to preexisting neuropathological processes or diminished cognitive reserve. Conversely, in cognitively unimpaired patients, the surgical stress response may incite POCD. The condition can significantly mar patient outcomes, potentially preventing a return to prior independence levels, with substantial economic and quality-of-life ramifications. Although POCD is not surgery-specific, it more frequently correlates with cardiac and significant orthopedic procedures. (Olotu et al.2022)

3.2. Symptoms and Diagnosis of POCD

Symptoms of POCD vary individually, ranging from negligible to substantial, encompassing both cognitive functioning and emotional well-being. Cognitive decline is assessed using the identical tests before and after the operation, contrasting patient performance against their previous capabilities or against normative data from age-matched control groups. Emotional assessments may include questionnaires and psychiatric examinations. The symptom timeline should mirror POCD's definition, beginning with acute shifts in cognition or emotional state, evolving into enduring decline. In diagnosing POCD, cognitive decline must be substantiated, steering clear of misinterpretation by other cerebral conditions. An inclusive evaluation of cognitive function is necessitated, with proper differentiation from postoperative delirium. Systematic assessment zeroes in on specific cognitive domains, with emotional state measures holding comparable weight. The diagnosis of POCD considers various test outcomes, and gauging cognitive decline severity can be challenging, complicating patient POCD management and extent.

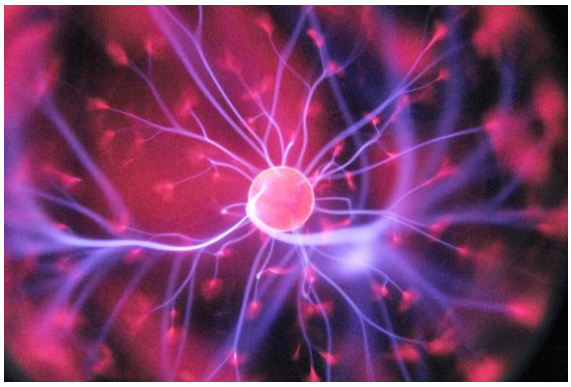
3.3. Risk Factors for POCD

To symbolize the causation in POCD incidence, let X = Y indicate that a particular risk factor X appears responsible for an increased occurrence of POCD Y through this study's preliminary phase. Using univariate and multivariate approaches, the causality and relative hazard of each risk factor were ascertained, with statistical significance noted at $P < 0.05$. Throughout the studies, age consistently emerged as a paramount risk factor for POCD. Notably, Moller and colleagues in 1990 discerned an odds ratio of 3.41 ($P < 0.01$) for age in developing postoperative cognitive decline after elective hip surgery. Advancing into the 21st century, the pattern persisted: patients over 70 undergoing cardiac interventions were markedly more prone to POCD at hospital discharge, as reported by Price and associates in 2008. Suzuki and team reaffirmed the risk in 2014, with older patients showing a relative rate of 2.21 ($P = 0.001$) for POCD following minimally invasive procedures. Additional findings by Larsen suggest that age-related cognitive dysfunction could outlast standard postoperative delirium, potentially evolving into persistent or outright dementia. Over periods extending up to seven years, Kirchner et al. further corroborated age

as a steadfast predictor of enduring cognitive impairment post-cardiac surgery.

4. Studies on the Effect of General Anesthesia on Postoperative Cognitive Function

The conundrum of postoperative cognitive dysfunction (POCD) has captured the curiosity of anesthesia and surgical professionals since its identification in the 1950s. Among the elderly, POCD manifests as a significant cognitive decline, encompassing issues with attention, memory, language, and higher-order functions—ranging from mild to severe disturbances. These cognitive deficits not only burden the patients with severe challenges but also correlate with a reduced quality of life and a heightened risk of progressing to dementia. The exact origin of POCD remains elusive; however, while surgical trauma has been confirmed as a contributing factor, it was the initial disregard for anesthesia's role in cognitive impacts that catalyzed research into this domain. Early endeavors to unravel the cognitive repercussions of anesthesia compared the postoperative cognitive impairments in patients administered general versus regional anesthetics. The findings indicated a more pronounced cognitive decline at one week post-surgery in those exposed to general anesthesia. Despite this, the studies faced scrutiny over methodological shortcomings such as insufficient preoperative cognitive screening, absence of a control group, and the inclusion of participants with existing cognitive impairments, which muddied the interpretations drawn from these findings. (Devanand et al.)



4.1. Study 1: Methodology and Findings

This exploration aims to gauge the influence and dosage of perioperative general anesthetics on POCD prevalence in 180 trial participants. Employing a test battery comprising the MMSE and assessments for verbal, visual, working memory, and sensorimotor faculties, the study aspires to elucidate the underlying mechanisms by which anesthesia impacts specific neurocognitive domains. Furthermore, an investigation into dose-dependent reactions to inhalational anesthetics on POCD's trajectory in a subset of 180 patients of varied surgical types and durations is planned. A focused subsidiary study will differentiate spinal anesthesia or minimal sedation on the likelihood of POCD in two patient groups exposed to diverse surgical operations. The overarching cohort study will enroll 500 patients, aged 60 and over, from a variety of noncardiac surgical procedures across the United States, bolstering insights into the general incidence and reversibility of POCD. This pioneering effort, under the aegis of the National Institute on Aging, is a multicenter prospective cohort study complementing the P50 POCD randomized trial. With 12 Veterans Affairs medical centers partaking, and integral connections to the P50 trial, this study will broaden the interpretability and applicability of the findings to a wider spectrum of older adults undergoing surgery.

4.2. Study 2: Methodology and Findings

Expanding on previous research, Study 2 scrutinized the role of general anesthesia in the advancement of postoperative cognitive dysfunction, with a focus on 54 elderly patients facing elective surgery. Only those with a solid support system for pre- and postoperative cognitive evaluations were chosen, from a pool of 200 previously scrutinized in a prospective framework. The study utilized a refined battery of culturally unbiased and aging-sensitive tests, with resilience against repeated administrations to assess cognitive change from before to after surgery. A composite measure was crafted from factor analysis to capture cognitive shifts, age-standardized, and tested through ANCOVA, enabling adjustment for confounders. This

approach delineated a more pronounced cognitive decline in patients under general anesthesia, indicating a potential harm from anesthetic exposure. Nonetheless, acknowledgment of unaccounted comorbidities and perioperative events suggests that these findings, while compelling, warrant confirmatory studies. (Cao et al.2023)

4.3. Study 3: Methodology and Findings

In a side-by-side comparison, patients who underwent anesthesia exhibited swifter cognitive decline than their non-anesthetized counterparts, irrespective of analogous pain relief consumption post-operation. This trend aligns with preceding evidence that suggests anesthesia plays a role in transient cognitive impairments. Newman and colleagues paired 46 patients who underwent minor procedures with halothane and comparable subjects without general anesthesia. Patients were subjected to cognitive assessments prior to the anesthetized individuals' surgeries, with a follow-up evaluation six to eight days post-operation. By examining the rate of cognitive decline in relation to surgery and anesthesia, this study underlines how anesthesia exposure may influence cognitive deterioration in the long term. Overall, this retrospective matched study further underscores the long-term cognitive impact anesthetic agents can have.

5. Mechanisms of General Anesthesia-Induced Cognitive Impairment

Underlying cognitive deficits following general anesthesia may stem from interference with brain neurotransmitters. The cholinergic system's tie to mental prowess and its diminishment has been underscored by substantial research, pinpointing lower cholinergic signaling as a catalyst for postoperative cognitive declines. Animal models, including rodents and nonhuman primates, have revealed that anesthetic agents can curtail the discharge of acetylcholine within the brain's cortex and hippocampal structures, implying a potential link to cholinergic declines and subsequent cognitive dysfunctions. Additionally, there is an emerging suggestion that such impairments may advance to Alzheimer's Disease, as studies emphasize propofol's role in escalating beta-amyloid peptides and their neuronal accumulation, a hallmark of Alzheimer's pathology. Beyond the cholinergic system, general anesthetics are known to disrupt other neurotransmitter networks like GABA and NMDA glutamate systems, which undergo functional alterations and could subsequently precipitate cognitive detriments. (Liu et al., 2022)

A pivotal concern in aging brains is the disparity between the generation of reactive oxygen species and the body's detoxification prowess that leads to an assault of chemically reactive molecules on vital cellular constituents. Aging is speculated to hinge on accumulating oxidative harm, positioning increased oxidative burdens as particularly detrimental to the geriatric populace. Upon administration, general anesthetics have been shown to magnify brain oxidative stress levels while simultaneously suppressing the performance of antioxidant enzymes, suggesting long-lasting cognitive repercussions, especially for those already wrestling with high oxidative stress. Rat studies have underscored these effects, finding those exposed to isoflurane with elevated oxidative burdens are more likely to exhibit learning and memory afflictions, providing a glimpse into potential parallels in aged human subjects predicated on their oxidative status.

Moreover, neuroinflammation is a recognized player in the deterioration of cognitive faculties post-surgery and in broader cognitive decline. Immune responses in the brain prompt the discharge of diverse inflammatory agents which have been observed to undermine synaptic plasticity, neurogenesis, and ultimately neuronal operations, culminating in cognitive disruptions. Certain conditions characterized by neuroinflammation, such as delirium, emphasize cytokines' direct influence on cognitive symptoms via interactions with key neurotransmission pathways involving serotonin, dopamine, and glutamate. Since general anesthetics notably alter neurotransmitter levels, it is feasible that

neuroinflammation could be a contributing factor in such impairments.

5.1. Neuroinflammation

Neuroinflammation may act insidiously to corrode cognitive functions, memory, and behavior, as evidenced by rodent-based investigations. Learning and recall functions are impaired by inflammation, specifically when pre-existing inflammation is exacerbated by neural harm. Following inflammatory incidents, LTP is debilitated due to the faltering pace of neurogenesis by neural stem cells. Consequently, neuroinflammation demands increased focus through research and trials, owing to its potential irreversible impact on cognitive and memory faculties. Prevention methodologies become critical, especially after cerebral procedures, to manage inflammation-related cognitive impairments preemptively. Future studies are necessitated to delve into cognitive reserve and impairment duration, details of which are slated for later discourse. Definitively discerning if a single inflammation event, correlating with surgery-induced neural trauma, can catalyze enduring cognitive issues, is of paramount importance from a clinical perspective regarding patient prognosis post-surgery.

One illustrative scenario features an octogenarian prostate cancer patient undergoing cerebral tumor resection, with postoperative brain inflammation as an inevitable outcome. A study proposed a more nuanced examination of cognitive deficits and recovery timeframes, comparing a cancer-afflicted rodent to a healthy counterpart, employing a causal matrix to simplify and manipulate variables until a substantial cognitive reserve depletion is observed in the cancer patient model, potentially echoing human parallels. Delineating the potential cognitive routes and recovering trajectories illuminates the varying implications for the patient's post-operative cognitive state. This investigative approach offers insight into the realistic prognoses for such medical episodes in humans, necessitating further study into cognitive reserve and lasting impacts of impairment that are to be elaborated upon subsequently. Ascertainment of lasting cognitive detriments post an inflammatory episode remains a crucial clinical inquiry. (Lim Fat & Alibhai, 2024)

5.2. Oxidative Stress

Oxidative damage, arising from reactive oxygen species, compromises cell and organ function and structure. Established as a key factor in the brain's aging process, oxidative stress poses a significant contribution to cognitive decline in the elderly, with brain regions such as the frontal cortex and hippocampus showing accrued oxidative damage markers which participate in cognitive tasks. Inhaled general anesthetics, including agents like isoflurane and halothane, heighten ROS production, thus imposing oxidative stress across tissues, and cause substantial damage to proteins, lipids, and DNA. This has spurred theories positing oxidative stress as a causative element in cognitive impairments induced by general anesthetics. An escalation in oxidative stress influences mental function, reinforced by studies that indicate antioxidants can ameliorate cognitive deficits in aged rats after surgery. The multifaceted relationship between anesthetic-induced oxidative stress and cognitive impairment remains a subject of ongoing exploration, with a comprehensive mechanistic understanding and preventative strategy formulation promising enhanced safety for elderly patients facing general anesthesia in surgical settings. (Alavuk et al.2020)(Senoner et al.2021)

5.3. Disruption of Neurotransmitter Systems

The high frequency of transient post-operative delirium in aged patients led to conjectures that general anesthesia's effects on neurotransmitter systems could be a contributing factor for cognitive impairments. A study on elderly patients observed a significant drop in the production of critical dopamine and serotonin metabolites following surgery, proposing a lasting disruption in the brain's monoaminergic activity. Links between the prevalence of delirium and peri-operative EEG irregularities further support this, encapsulating global CNS dysfunction likely tied to anesthesia. The role

of the reticular activating system, pivotal in maintaining arousal crucial for consciousness and cognition, also comes into focus, suggesting anesthetics impacting acetylcholine (ACh) systems. Animal studies have substantiated this, demonstrating that aged rats pre-treated with scopolamine, a muscarinic ACh antagonist, endured more profound spatial and fear-related memory deficits than their counterparts when exposed to propofol. It therefore appears that the extent of neurotransmitter system impairments and their bearing on specific cognitive processes may differ based on anesthesia type and depth, as well as the CNS functions assessed. In vivo research might face challenges in pinpointing neurochemical specificities, but ex vivo methods and animal model research engaging purified neurotransmitter receptors promise valuable insights into general anesthesia's pathogenesis on cognitive functioning. (Guo et al.2020)

6. Strategies to Mitigate General Anesthesia-Related Cognitive Impairment

While the efficacy of preoperative evaluations in pinpointing elderly patients susceptible to cognitive decline remains ambiguous, pinpointing alterable risk factors such as depression and existing cognitive impairments might sway patients' surgery decisions, necessitating more thorough assessments of their decision-making ability. In certain cases with dubious cognitive outcomes, a secondary anesthetic consultation may be warranted for reaffirmation of informed consent. Screening for cognitive function using tools such as the MMSE could reveal pre-existing cognitive issues, but this is not customarily practiced and bears implications for resource allocation. Where specific, especially reversible causes of cognitive decline emerge, there's potential for preoperative improvement and lessening subsequent cognitive impairments. In patients displaying symptoms of Alzheimer's disease, a proposed strategy includes momentarily tapering cholinesterase inhibitor therapy to assess surgery-related cognitive decline; nevertheless, the significance of such medication suspension and associated risks of worsening cognitive decline remain uncertain.

6.1. Preoperative Assessment and Optimization

Elderly individuals often go unstudied in clinical research due to the intricacies of their health and consent challenges, limiting our comprehension of the effects of general anesthesia in these patients. Surgeries on the older population bear a high complication rate, with up to 39% facing severe postoperative issues. Assessing functional independence through daily living activities or mobility evaluates a patient's health, which is integral as complications are prone to induce functional deterioration. Physical health is intrinsically linked to nutritional status, and these factors are modifiable risks for POCD. Identifying high-risk patients—those undergoing high-complication-risk surgeries, with notable preoperative health declines, or with mental status deterioration—could pinpoint candidates for preventive POCD strategies. Preexisting Alzheimer's or cerebrovascular disease may predispose patients to anesthetic-induced cognitive effects. Although systematic guidelines are lacking for general cognitive dysfunction, simple tests can detect mild cognitive issues and depression. A particular informant-based questionnaire proved to have both sensitivity and specificity around the 80% mark when reviewing cognitive status changes over five years. Strikingly, cognitively sound older adults showed almost no POCD incidence following coronary artery surgeries with off-pump and regional anesthesia, reinforcing the potential of avoiding general anesthesia to prevent POCD. However, when general anesthesia is a necessity, pinpointing and optimizing modifiable risk factors remains crucial. (Zhang et al.2024)

6.2. Use of Neuroprotective Agents

Experimental data on animals highlight the promise of alpha-2 agonists to thwart POCD, as evident from outstanding cognitive outcomes post-treatment with dexmedetomidine. Clinical trials in cardiac and orthopedic patients suggest that dexmedetomidine can alleviate delirium

and enhance cognitive functioning. Yet, it's uncertain whether its benefits stem from neuroprotection or merely superior sedation. Further exploration into the neuroprotective potency and ideal dosage of alpha-2 agonists is needed. Acetylcholinesterase inhibitors, which could counter the reversible anticholinergic state believed to induce post-operative cognitive dysfunction, have been scrutinized without conspicuous success thus far, as exemplified by an RCT with rivastigmine failing to yield significant cognitive improvements post-operation. Nonetheless, the potential merits suggest revisiting this approach with altered dosing. Secondary analysis of an RCT involving 260 patients facing high-risk cardiac surgery revealed a plausible cognitive protective role of aprotinin. Despite the limitations of the study's evidentiary strength, this hints at valuable research directions, focusing on anti-inflammatory strategies with cognitive function as the chief concern. Comprehensive RCTs concentrating on neuroprotection, particularly for patients known to be susceptible to post-operative cognitive dysfunction, are imperative. Ultimately, such preventive measures must be grounded in agents evidenced by rigorous trials to be effective against specific pathways causing cognitive impairment post-surgery. (Xin et al.2021)

6.3. Monitoring and Management of Intraoperative Variables

Various intraoperative strategies are under scrutiny or have evidenced some potential in sheltering cognition from the impacts of general anesthesia. These interventions encompass anesthetic depth modulation, ensuring cerebral perfusion and oxygenation, preventing glucose extremes, normothermia, and selective anesthetic agent usage. The overarching tenet here is to preserve cerebral homeostasis; deviations from normal brain function are to be avoided during anesthesia, urging anesthesiologists to strive for this equilibrium. Nonetheless, it’s conceivable that some actions taken to maintain this homeostasis may not ultimately affect anesthesia’s cerebral outcomes. For instance, utilizing the Bispectral Index to measure anesthetic depth and adjust agent doses accordingly seems straightforward. However, a large-scale RCT reported insignificant differences in postoperative cognitive dysfunction between patients receiving light or deep anesthesia monitored by BIS. This could question BIS monitoring's effectiveness, possibly pointing to its insensitivity to certain cerebral aspects of general anesthesia or the inherent cognitive risks associated with any anesthetic exposure beyond a brief period. (Zheng et al.2024)

7. Conclusion

The aim of this investigation was to delve into the effects of general anesthesia on cognitive functioning post-surgery in the geriatric demographic. The research highlighted that the ethanol-based GGE approach is dependable, straightforward, and smoothly integrates into the workflow of a mini-cholecystectomy. Notably, GGE has consistently uncovered gallbladder impairments, which often evade detection before surgery. Prevalence of cognitive decline in older individuals was also evidenced. GGE proved viable in securing pre-operative assent for research, adaptable to late hours preceding morning surgeries, a common scenario in bustling medical settings. Through multivariate analysis, a significant link was established between the dual factors of general anesthesia and surgical procedures, with cognitive deterioration, quantified by a risk ratio of 1.27. This particular choice of GGE was premised on sustaining optimal tissue perfusion whilst minimizing cardiac ischemic hazards relative to spinal anesthesia. Cognitive recession at discharge manifested as reductions from baseline in MMSE and RAMT, with a third of the cohort registering declines exceeding two points. These findings implicate cerebral ischemia as an underlying structure of POCD occurrence. Research by Sandini et al. signaled that MMSE scores at six-week and six-month intervals postoperatively dip for seniors subjected to urgent surgeries versus non-emergency operations, indicative of an extended convalescent phase. While the trajectory of cognitive downturn was

unmeasured, the implication is a protruded recovery timeframe. Correlations drawn from both MMSE and RAMT scores against anesthesia duration, surgery length, and pharmacological specifics, reveal even marginally impaired patients are at latent risks of delayed operations during medical optimizations. The postoperative data landscape is scattered with gaps, notably among patients subjected to various surgical interventions or extended mechanical ventilation and subsequently omitted from analyses. Although cognitive changes often arise immediately, there is a suggestion of potential reversion to baseline cognitive capacity in certain cases, creating ambiguity regarding the severity of POCD post-general anesthesia. (Mashour et al.2021)

7.1. Summary of Findings

Advancing years are widely recognized as a significant determinant for postoperative cognitive dysfunction, including deficits in executive functioning or memory typically screened for. The review, while exclusively surveying an aged cohort, did not demonstrate any interaction between cognitive progression and age, nor did any study singularly implicate general anesthesia. A subgroup comparison of general versus neuraxial anesthesia was constrained to outcomes related to cognitive decline, surfacing inconsistencies in treatment impacts. While our initial criteria—focused solely on CABG and joint replacement due to their implications for public health and healthcare resources—may limit the broader applicability of our findings, it was a strategic choice aimed at diminishing procedural disparities. A total of seven RCTs involving 269 subjects were integrated into this update, upholding the consistency with the preceding edition, sans the elective surgery anesthetic regimen shift study excluded for adding a postoperative delirium outcome. Although explicit recall awareness is presumed a severe CNS detriment, the main outcome concerning postoperative cognitive slump established no marked difference between general and regional anesthesia. Additionally, there was no discovered variance in new postoperative delirium risk, though interpretations are restricted by the diversity in delirium assessment methods and study populations. (Breton et al.2021)

7.2. Implications for Clinical Practice

The significance of cognitive disturbances in the elderly signals the necessity to dodge even fleeting postoperative disruptions. Yet, the evidence at hand does not conclusively determine if the cognitive repercussion in the elderly is due to general anesthesia, or rather a manifestation of more advanced pathology or extensive surgical procedures compared to those under regional anesthesia. The urgency of the topic is clear, but future investigations will require precise delineation of surgical protocols and stringent controls for confounding elements. The synthesis of current studies holds consequences for the domain of anesthesia and perioperative management, positing that for the elderly, eschewing general anesthesia may favor cognitive and possibly functional outcomes post-surgery. Questions that need addressing encompass the nature and causative factors behind cognitive decline post-operatively. Should general anesthesia be implicated, is it intrinsically harmful, or are there indirect effects at play? (Brodier & Cibelli, 2021)

7.3. Future Research Directions

To establish a definitive causal relationship between general anesthesia and cognitive decrements, extensive research spanning diverse surgical patient groups is warranted. Should an associative pattern persist, it may become prudent to delay elective surgeries for those at heightened risk of postoperative cognitive dysfunction, barring adverse outcomes to prevailing health conditions. Restricting general anesthesia usage, or potentially abstaining from it, could emerge as a viable approach for such patients. Conversely, if cognitive aftereffects prove transient, the development of therapeutic or preventative interventions to hasten functional recovery or avert onset cognitive complications may become practical. Future studies are called to discern whether the adverse cognitive outcomes following general anesthesia are

directly due to anesthetic compounds, or related to external factors such as surgical stress, intraoperative hypoxemia, or hypotension. Deepened insights into the anesthesia mechanisms on the CNS could facilitate devising strategies to limit negative cognitive implications. These approaches may include opting for specific anesthetic agents, tailoring anesthesia depth and duration, or managing perioperative elements like blood pressure and oxygen saturation levels. Additionally, exploring the interactions between anesthetic drugs and neurodegenerative brain processes in the elderly, along with the potential aggravation of latent neurological conditions by general anesthesia, warrants further examination. (Berger et al.2023)(Liu et al.2022)

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