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Abstract

Postoperative cognitive dysfunction (POCD) and postoperative delirium (POD) are of concern in the elderly population undergoing an anesthetic due to increased mortality and decreased quality of life that can ensue. Sui et al. (2021) reported a 15-50% incidence of POD in elderly surgical patients. Dexmedetomidine is a highly selective, alpha-2 agonist with sedative, analgesic, and anxiolytic properties that mimics a sleep-like state and causes bradycardia and hypotension but not respiratory depression. Dexmedetomidine has neuroprotective properties, including anti-apoptosis and anti-inflammation (Wu et al., 2019). A current review of the literature revealed that dexmedetomidine use can decrease POD incidence in the aged patient population undergoing general anesthesia. Intraoperative or postoperative dexmedetomidine use should be considered in the elderly patient receiving general anesthesia.

keywords: delirium, postoperative delirium, postoperative cognitive dysfunction, elderly, aged, dexmedetomidine

The Impact of Dexmedetomidine Use in Patients Over the Age of 60 Undergoing General Anesthesia on Postoperative Delirium Incidence

Delirium is the most common postoperative complication in the elderly, with an incidence of up to 54% (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015; Li et al., 2020; Subramaniyan &Terrando, 2019). Implications of delirium are serious and impact the patient, their families, healthcare givers, and society. Oh et al. (2017) reported that delirium is responsible for an annual cost of 164 billion United States dollars, and it affects over 2.6 million patients per year. Dexmedetomidine has been used successfully to decrease emergence delirium in pediatric patients, prompting worthwhile research into its use in the adult and aged populations (Li et al., 2020). Dexmedetomidine has been shown to decrease delirium, improve sleep quality in adults admitted to the intensive care unit (ICU) after surgery, and improve quality of life, cognitive function, and long-term survival at a three-year follow-up (Wu et al., 2019).

This paper will discuss what delirium is, how it is assessed, its implications, how surgery and anesthesia contribute to delirium development, and known interventions to decrease delirium. A brief overview of POD, POCD, and dexmedetomidine will follow. A literature review of the effect of dexmedetomidine use in elderly patients undergoing surgery and its effects on postoperative delirium was performed. The literature search was conducted several times using PubMed, Embase, and Cochrane Collection Plus databases through the University of New England access. A review of the literature sought out original studies and systematic reviews with meta-analyses examining POD or POCD incidence when dexmedetomidine was used perioperatively in the aged population, identified as people over the age of 60. Several articles examining neurocognitive disorders, the pharmacology of dexmedetomidine, its role as a neuroprotective agent, and strategies in preventing and treating POD or POCD were also included. Ten original trials and 12 systematic reviews with meta-analyses published in 2016 or later were included in this literature review to examine relevant findings for meaningful implications for clinical practice for our aging population. Articles solely examining postoperative dexmedetomidine use, evaluating dexmedetomidine as a secondary agent in combating POD, studies in which POD was a secondary outcome, and those with neuraxial anesthesia as the primary anesthetic were excluded. The literature focused on methods of dexmedetomidine administration, cardiac versus noncardiac surgery types, and outcomes of dexmedetomidine use in the elderly population undergoing surgery.

Delirium

What is Delirium?

Delirium involves acute changes in the patient's level of consciousness, awareness, attention, memory, and recognition. Variations in the patient’s assessment and sleep-wake cycle disturbances are common in delirium. Neurotransmitter imbalance affects cortical and subcortical activity, including that at the reticular activating system, playing a role in the symptoms seen in delirium (Migirov et al., 2021). The inflammatory cascade elicited by surgery could impact the brain’s cognitive functioning contributing to the symptoms seen in delirium (Zeng et al., 2019). Genetics, neurotransmitter levels, electrolyte, and/or metabolic imbalances can also be implicated in the development of delirium (Zeng et al., 2019). Hypoactive, hyperactive, and mixed types of delirium exist (Deiner et al., 2017; Janssen et al., 2019; Qin et al., 2021; Migirov et al., 2021; Vlisides & Avidan, 2019). Hypoactive delirium is seen as a lethargic state and is often underdiagnosed in more than half of the actual cases (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015; Janssen et al., 2019; Migirov et al., 2021).

Hypoactive delirium appears with slowed alpha waves on EEG studies (Migirov et al., 2021; Vlisides & Avidan, 2019). Delirium is not diagnosed in 60% of the cases by the patient's primary caregivers but rather by "expert assessors" such as psychiatrists, geriatricians, neurologists, and those providers with extensive training in delirium assessment (Oh et al., 2017, p. 1161). This inaccurate assessment could be due to the constraints of standardized screening tools, especially when utilized once per day. Oh et al. (2017) indicated that patient interviews and chart reviews will increase the sensitivity and specificity of diagnosing delirium. Postoperative delirium onset can occur within hours to days after surgery. Because of the timing of the inflammatory processes during surgery, POD primarily presents two to three days postoperatively, causing the neurocognitive changes seen in delirium (Lee et al., 2018). Postoperative delirium can be diagnosed within a week of surgery or before discharge per the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM), fifth edition (Wang et al., 2021)

Postoperative cognitive dysfunction encompasses changes in cognition affecting memory, mood, communication, and sleep. This dysfunction presents after anesthesia and can last for weeks to months. Where delirium is a temporary state, POCD is longer lasting. Postoperative cognitive dysfunction implications can vary from prolonged hospitalization to difficulty communicating, decreased intelligence, personality change, self-care limitation, and it can lead to Alzheimer's disease (Carr et al., 2018; Yang et al., 2019; Zhou et al., 2016). Diagnosis of POCD is difficult due to the slow onset, its variation in symptoms, and the lack of standard criteria (Wu et al., 2019). The incidence of POCD is estimated to be 10-12% (Yang et al., 2019). Liu et al. (2015) shared that 38% of patients with acute delirium had a diagnosis of Alzheimer's disease two years later. Van Norden et al. (2021) contributed that 25% of patients diagnosed with delirium will experience symptoms comparable to those of mild Alzheimer’s disease, and that up to 70% of elderly patients over the age of 65 years who have experienced postoperative delirium will have an eventual diagnosis of dementia.

Screening Tools for Delirium

Many studies included in this literature review utilized the Confusion Assessment Method (CAM) or CAM modified for the intensive care unit (CAM-ICU) screening tool to assess patients for delirium. The CAM is a standardized, well-accepted, and widely used screening tool. Liu et al. (2015) and Oh et al. (2017) detailed the CAM-ICU assesses patients for delirium using the following data categories: altered mental status from baseline, inattention, disorganized thinking, and an altered level of consciousness. The patient must screen positive for the first two criteria listed and either disorganized thinking or an altered level of consciousness for a positive diagnosis utilizing this tool. Despite the common use and acceptance of the CAM, Vlisides and Avidan (2019) pointed out that CAM and CAM-ICU are inferior to "expert-based delirium identification" (p. 3). Vlisides and Avidan (2019) further revealed that these experts may differ on their delirium assessment, possibly stemming from the inconsistencies found in different editions of the DSM. These authors shared a study that found delirium was diagnosed in only 30% of the cases when the DSM-IV criteria were used versus the updated DSM-V criteria (Vlisides &Avidan, 2019). In addition to this diagnostic discrepancy, the authors identified potential gaps in educating healthcare workers on the appropriate screening tools and the implementation of delirium management protocols. This potential area for improvement in staff education highlights the concern that delirium is not being adequately identified and, therefore, may be potentially underreported and undertreated.

Oh et al. (2017) provided that the CAM has a high sensitivity, specificity, and interrelated reliability. Halpin et al. (2020) cited a 95% sensitivity and an 89% specificity for the CAM-ICU tool. Janssen et al. (2019) performed a systematic review and meta-analysis including 31 randomized control trials (RCTs) and four before and after studies looking at prevention strategies for POD prevention in elderly patients. Over half of the studies included in Janssen et al. (2019) utilized CAM to assess the participants for delirium. Lee et al. (2019) validated CAM-positive patients with a psychiatrist's diagnosis. Lin et al. (2021) identified 21 RCTs evaluating the use of dexmedetomidine for delirium prevention in elderly patients over the age of 60 undergoing various types of surgery. Each of these reviewed studies utilized the CAM or CAM-ICU. Qin et al. (2021) performed a systematic review and meta-analysis of 13 RCTs studying the effect of perioperative dexmedetomidine use on delirium prevention in adults over 18 undergoing noncardiac surgery. Each of these RCTs utilized the CAM or CAM-ICU assessment to screen for delirium like the majority of the articles included in this literature review. The CAM and CAM-ICU screening tool remains a standardized, well-known, and frequently used assessment method for delirium in healthcare settings.

The Mini- Mental State Exam (MMSE) was utilized in 13 studies analyzed by Carr et al. (2018) and it was determined that this tool inaccurately identified dementia, particularly in outlying patient populations, including the aged, less educated, and those with different cultural backgrounds. Zhang et al. (2018) identified the MMSE is best used for serious cognitive dysfunction, and assesses the patient on orientation, memory, calculation, language, visual-spatial ability application, and attention. The higher the score on the MMSE, the less severe the cognitive impairment. The MMSE is used to screen patients for cognitive impairment but was initially created to assess cognitive deficits in the patient with an established diagnosis of dementia (Migirov et al., 2021). The MMSE excluded patients with underlying cognitive dysfunction in Li et al. (2021). Deiner et al. (2017) assessed the participants in their study using the CAM-ICU screening tool in the recovery room to assess for POD but also utilized the Delirium Symptom Interview in conjunction with the MMSE to assess their participants allowing for higher sensitivity and specificity and the ability to identify delirium occurrences in between assessments. Zhou et al. (2016) were interested in participants' MMSE scores when reviewing studies that measured intraoperative dexmedetomidine use and the incidence of POCD. Mini-Mental State Exam scores were measured to determine the severity of POCD in the cardiac and noncardiac studies included in the systematic review and metanalysis undertaken by Yang et al. (2019).

The Montreal cognitive assessment (MoCA) is best utilized for assessing patients with mild cognitive dysfunction per Zhang et al. (2018). The MoCA assesses visual space function, language, attention, calculation, recall, and abstract thinking by patients. Migirov et al. (2021) shared the MoCA is a more sensitive test than the MMSE in detecting postoperative neurocognitive disorders per the results of a systematic review and cautioned the reader that the MoCA does not take into account the patient's level of education and lacks cultural generalizability.

Implications of POD and POCD

Postoperative delirium is distressing for the patient, their families, and hospital staff. Postoperative delirium is associated with increased mortality, prolonged hospital stay, decreased incidence of returning to independent living, increased healthcare costs, and cognitive and functional decline (Deiner et al., 2017; Duan et al., 2018; Liu et al., 2016; Pan et al., 2019; Shi et al. 2019; Vlisides & Avidan, 2019; Xin et al., 2021). Postoperative cognitive dysfunction can cause changes in memory, impair intellect, impact personality, and the ability to interact with others and to care for oneself. Postoperative cognitive dysfunction impacts individuals, families, and society.

Risk Factors for POD and POCD Development

Delirium is a complex acute state with multiple contributing factors. There is a higher risk of incidence in patients with preexisting cognitive impairment (Vlisides and Avidan, 2019; Xin et al., 2021). Additionally, preoperative cognitive function is the most significant factor for POD risk (Wu et al., 2019). Janssen et al. (2019) identified frailty, advanced age, preexisting cognitive deficits, malnutrition, polypharmacy, pain, length of stay, blood loss, preoperative anemia, indwelling urinary catheters, and type of surgery as predisposing risk factors for delirium development. In general, cardiac surgery and the use of the cardiopulmonary bypass machine increases the risk of postoperative neurocognitive deficits (Duan et al., 2018; Migirov et al., 2021). Inadequate pain control contributes, as does the use of morphine due to its neurotoxic properties (Shi et al., 2019).

The risk factors for POCD are similar to those for POD. Advanced age, delirium duration, preexisting cognitive impairment, type and duration of surgery, return to the operating room, postoperative infection, mechanical ventilation, hypertension, the use of benzodiazepines, and educational level are risk factors for POCD development (Yang et al., 2019; Zhou et al., 2016). Zhou et al. (2016) identified that cardiac surgery has been definitively linked to increased incidence of POCD, whereas hypotension, depth of anesthesia, and elevated cortisol levels have been postulated to impact increased incidence directly. Liu et al. (2016) identified that lengthy periods of POD have been linked to POCD development. Conversely, regional anesthesia has been associated with decreased incidence of POCD (Zhou et al., 2016).

Known Interventions to Decrease Delirium

Numerous authors agree that prevention is necessary with our aging population and the high incidence of POD and POCD. Janssen et al. (2019) revealed that 30 to 40% of delirium cases are preventable, and once delirium sets in, treatment does very little to decrease the duration, severity, or recurrence. It is imperative to mitigate preventable risk factors, including pain management, utilization of sensory devices, and optimizing nutritional status and sleep schedule. Janssen et al. (2019) performed a systematic review looking at studies that had an intervention to decrease POD. Thirty-one RCTs and four before and after trials were analyzed. The authors categorized the findings according to the phase of care along the perioperative continuum that the intervention was performed. Conclusively, several strategies, including the use of multicomponent interventions like the Hospital Elder Life Program (HELP), antipsychotic medications, anesthesia depth guided by bispectral index (BIS), and the use of dexmedetomidine, were successful in decreasing POD incidence.

Vlisides and Avidan (2019) described similar effective management strategies in three significant trials looking at anesthetic depth and postoperative delirium. In the Cognitive Dysfunction after Anesthesia (CODA) trial, a BIS guided anesthetic depth in 902 participants undergoing general anesthesia with either inhaled agents or propofol. In this landmark trial conducted by Chan et al. (2013), the randomly assigned BIS-guided group was compared to a standard care, control group in which the patients had a BIS in place for data collection, but providers were unaware of this BIS data. Participants' neurocognitive function was assessed one week before surgery, one week after surgery, and three months postoperatively. Patients were assessed daily with the CAM for delirium. There was a 35% decrease in delirium incidence during hospitalization and a 31% decrease in POCD three months after surgery in the BIS-guided group. Furthermore, anesthetic depth guided by a BIS to a level of 40 to 60 resulted in a 20% reduction in propofol dose delivery and a 30% reduction in volatile anesthetic administration (Chan et al., 2013).

In the second referred study, the Surgery Depth of Anaesthesia and Cognitive Outcome trial, 1277 elderly patients undergoing noncardiac surgery with volatiles or propofol were either BIS-guided or BIS-blinded. There was a 16.5% incidence of POD in the BIS-guided compared to 21.4% in the BIS-blinded group. Vlisides and Avidan (2019) pointed out early trial conclusion was due to a lack of funding, and a portion of the BIS-blinded group was unblinded for some part of the study. Despite these limitations, Vlisides and Avidan (2019) indicated that this study, along with the CODA trial, supports the thought that EEG suppression and deep anesthesia are associated with POD. Li et al. (2020) presented this correlation between deep anesthesia and an increased likelihood of delirium incidence and inferred that a decreased level of anesthesia could be achieved using a BIS. Vlisides and Avidan (2019) described the Electroencephalopathy Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial looked particularly at avoiding EEG suppression in BIS-guided participants versus BIS-blinded participants. This trial did not support the notion that deep anesthesia is a direct causative factor for POD, as delirium occurred in more patients who received BIS monitoring and adjusted anesthesia than in the control group. In line with the ENGAGES trial, the Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients trial looked at aged patients undergoing hip surgery and POD incidence in light and heavy sedation combined with spinal anesthesia. There was no difference in POD based on the level of sedation received (Vlisides & Avidan, 2019). The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults (2015) detailed an inadequate amount and low-quality evidence on the using a BIS guiding a low anesthetic depth and its direct effect on POD incidence. Despite these two trials, the consensus in the literature is that the risk of delirium could be decreased when the least amount of adequate anesthesia is administered (Janssen et al., 2019; Oh et al., 2017). Migirov et al. (2021) and the American Geriatrics Society Expert

Panel on Postoperative Delirium in Older Adults (2015) recognized the utilization of EEG device assisted anesthetic monitoring in guiding anesthetic depth but caution against the risk of light anesthesia consequences, concern for overreliance on BIS or EEG indices as single data points, as well as the lack of long-term results of EEG-guidance on postoperative cognitive function, thus encouraging the need for further, more definitive research.

Multicomponent interventions like the HELP involve multiple disciplines that employ strategies to preserve functional status and cognition in hospitalized elderly patients. The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults detailed multicomponent nonpharmacological interventions such as promoting mobility and sleep quality, visual and auditory aids, optimizing fluid and nutritional status, pain management, and avoidance of infection and hypoxia. Vlisides and Avidan (2019) reported decreased POD incidence and healthcare costs with the HELP utilization based on a meta-analysis of 14 studies. Janssen et al. (2019) reviewed six studies that implemented a multicomponent intervention program similar to the HELP, four of which decreased delirium incidence.

Oh et al. (2017) conducted a literature search on delirium diagnosis and treatment from 2011 to 2017. This article included guidelines targeting the prevention and the treatment of POD in the elderly in the perioperative period released by the American Geriatric Society and the American College of Surgeons in 2014. Oh et al. (2017) detailed seven strong recommendations, the following: (1) appropriate continuing education for healthcare staff, (2) pre-assessments performed to identify potential risk factors for delirium, (3) multicomponent nonpharmacological interventions for patients at risk for delirium, and (4) adequate analgesia planning with emphasis on nonopioid medications. Furthermore, (5) antipsychotics and benzodiazepines should be avoided in the hypoactive delirium patient, and (6) agitation should not be initially treated with benzodiazepines in patients with delirium. The last recommendation (7) included avoidance of medications that can contribute to delirium, including anticholinesterases, opioids, benzodiazepines, antihistamines, dihydropyridines (Oh et al., 2017). Weak recommendations included using regional anesthesia when possible to decrease postoperative pain and delirium and the use of the lowest possible effective dose of antipsychotic medications for the shortest possible time in delirious patients who are a risk to themselves or others. Lastly, multicomponent nonpharmacological interventions can be used to prevent POD and treat the patient who has already been diagnosed with POD (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015; Oh et al., 2017). Ultimately, Oh et al. (2017) urged that preventing and managing delirium with a multicomponent nonpharmacologic approach is the safest and most effective strategy.

Inflammatory Response to Surgery Effects

Lee et al. (2018), Li et al. (2020), Migirov et al. (2021), Zeng et al. (2019), Zhang et al. (2018), and Zhou et al. (2016) recognized the role of inflammation from anesthesia and surgery on the development of POD and POCD. There is evidence that brain interleukin (IL-6), tumor necrosis factor (TNF-α), and S100 ß protein are increased by anesthesia and surgery (Zhang et al., 2018). Activated IL-6 and TNF-α are adaptive and innate immunity cytokines associated with the hyperactive form of delirium (Migirov et al., 2021). Surgical stress increases cortisol production, which in turn causes IL-6 release. Lee et al. (2018) measured IL-6 levels in participants older than age 65 undergoing laparoscopic surgery at one and 24 hours after surgery, finding significantly lower levels in those who received dexmedetomidine versus those who received saline. Lee et al. (2018) postulated that patients who received dexmedetomidine were less likely to develop POD because of this decreased inflammatory response finding. Govêia et al. (2021) cited several other research articles in which dexmedetomidine decreased IL-6 and TNF-α levels supporting dexmedetomidine's anti-inflammatory properties. Zhang et al. (2018) identified S100 ß protein as an indicator of central nervous system injury, and elevated levels were correlated to brain injury and could be associated with POCD incidence. Govêia et al. (2021) connected that dexmedetomidine's neuroprotective qualities were attributed to its ability to decrease S100 ß protein and neuron-specific enolase levels, thereby protecting the patient from postoperative cognitive and behavioral dysfunction.

Dexmedetomidine Pharmacology

Multiple authors, including Carr et al. (2017), Liaquat et al. (2021), and Yang et al. (2019) described dexmedetomidine as a selective alpha-2 adrenergic agonist that has sedative, analgesic, anxiolytic, and sympatholytic effects. Dexmedetomidine decreases sympathetic nervous system activity, potentially causing bradycardia and hypotension. This drug causes a dose-dependent decrease in catecholamine release in the central nervous system. Sedation occurs in the locus coeruleus (Yang et al., 2019). Dexmedetomidine creates a stage two, sleep-like state where respiratory function is preserved, and the patient remains arousable. Dexmedetomidine allows for decreased opioid consumption because of its action at the alpha-2 adrenergic receptor (Carr et al., 2018; Govêia et al., 2021; Pan et al., 2019).

Carr et al. (2018), Nagelhout & Elisha (2018), and Liaqat et al. (2021) detailed that alpha-2 receptors are G-protein coupled receptors that when activated, decrease the production of adenylyl cyclase, and in turn decrease the amount of cyclic adenosine monophosphate (CAMP) available, therefore leading to a decrease in cell excitability. Activation of the G-protein coupled receptors hyperpolarizes the cell via the opening of potassium channels, accounting for a decrease in protein and catecholamine release. Calcium influx is inhibited by G protein-coupled receptor activation which limits protein kinase C formation, decreasing its contribution to oxidative stress and apoptosis. Dexmedetomidine's action at the presynaptic neuron decreases the release of the neurotransmitter norepinephrine. Dexmedetomidine produces a dose-dependent sedative effect and decrease in BIS values. Dexmedetomidine does not impact cerebral metabolism but causes cerebral vasoconstriction, lowering cerebral blood flow (Nagelhout & Elisha, 2018).

Dexmedetomidine is a short-acting sedative with an onset of action of 10 to 20 minutes, a distribution half-life of six minutes, and a 10 to 30-minute duration of action when stopped. Dexmedetomidine is metabolized by the liver and excreted in the kidneys relatively unchanged and is highly protein-bound (Nagelhout & Elisha, 2018). Dexmedetomidine regulates neuroinflammation, apoptosis, oxidative stress, and synaptic plasticity, providing neuroprotective properties. Dexmedetomidine works centrally in the medulla oblongata to decrease the sympathetic nervous system response, thus impacting the neuroendocrine stress response to surgery (Carr et al., 2018). This mechanism also decreases shivering (Nagelhout & Elisha, 2018). As discussed above, the body's inflammatory response to surgical stress can be mitigated by dexmedetomidine's neuroprotective effects (Govêia et al., 2021; Lee et al., 2018; Zhang et al., 2018).

Literature Review

Dexmedetomidine and POD

Noncardiac Surgeries

Dexmedetomidine and its impact on POD were studied in several well-designed RCTs in elderly patients undergoing noncardiac types of surgery. Five of the six original RCTs showed intraoperative dexmedetomidine decreased the incidence of POD. Saline was used in the control group of five original trials examining intraoperative dexmedetomidine administration (Deiner et al., 2017; Lee et al., 2018; Li et al., 2020; Liu et al., 2016; Xin et al., 2021). One RCT, conducted by Zhang et al. (2018), compared an anesthetic consisting of dexmedetomidine with either propofol or sevoflurane to an anesthetic consisting of midazolam with either propofol or sevoflurane. Of these five original trials that showed that intraoperative dexmedetomidine decreased the incidence of POD, one by Liu et al. (2016) and the other by Xin et al. (2021) solely investigated patients with baseline mild cognitive impairment (MCI), while Deiner et al. (2017) included patients with baseline MCI in their study. Delirium assessment was performed either twice per day on postoperative days one through five or on postoperative days one, three, and seven in all original studies except that performed by Denier et al. (2017) validating the results.

In a landmark trial, Deiner et al. (2017) conducted a ten-center, double-blinded, parallel-group, placebo-controlled RCT involving 404 patients over 68 years old undergoing major noncardiac surgery. This trial utilized dexmedetomidine on arrival to the operating room (OR) and continued the infusion until two hours postoperatively, whereas the control group received saline. The authors assessed the patient's preoperative cognitive function, assessed for POD with the CAM or CAM-ICU, performed a three month follow up, and performed a six month follow up to compare cognitive scores to baseline scores. There was no difference in severity between groups or subtypes of delirium. In fact, the incidence of POD was the same in both the control and study groups. In this study, there was a relationship in patients with lower education status and baseline MCI to POD, but not with POCD. Dexmedetomidine administration had no impact on postoperative cognitive outcomes at three and six months postoperatively. This original trial was cited by or included in the systematic review and meta-analyses by Duan et al. (2018); Lee et al. (2018); Li et al. (2020); Lin et al. (2021); Pan et al. (2019); Qin et al. (2021); Xin et al. (2021); van Norden et al. (2021); Zeng et al. (2019); and Wang et al. (2021). These other authors are critical of this original study by Denier et al. (2017) as POD was only assessed once per day and initially began in the post anesthesia care unit (PACU).

Li et al. (2020) performed a double-blind RCT involving 260 patients over 60 years old undergoing major noncardiac surgery. Participants were randomized to receive either a loading dose of dexmedetomidine before induction followed by continuous infusion until one hour before the end of the surgery or participants received volume matched normal saline. The CAM or CAM-ICU was used to assess patients for POD during the first five days postoperatively. A BIS was utilized intraoperatively to guide anesthetic depth, and anesthesia was maintained with intravenous (IV) propofol, sufentanil, and 1:1 oxygen to nitrous oxide. Dexmedetomidine halved the risk of POD in adults over the age of 60 years undergoing major noncardiac surgery. Dexmedetomidine was associated with a lower rate of acute agitation, perioperative tachycardia, early postoperative nausea and vomiting (PONV), and non- delirium complications 30 days after surgery. A morphine PCA was used postoperatively in this study, a distinction that is important as opioids have been shown to contribute to POD incidence and severity.

Cardiac Studies

Three original RCTs in elderly patients undergoing cardiac surgery were found and included in this review. In the double-blinded, randomized, placebo-controlled, multi-center trial conducted by Li et al. (2017), 285 adults over the age of 60 years undergoing elective coronary artery bypass grafting (CABG) and/or valve replacement received either dexmedetomidine or saline initiated at 0.6 mcg/kg over 10 minutes then 0.4 mcg/kg/hr until the end of the case. After surgery, the medication was continued at 0.1 mcg/kg/hr. Patients could receive preoperative medications, and general anesthesia was maintained with either total intravenous anesthesia (TIVA) consisting of sufentanil and propofol, or with sevoflurane, both methods with a target BIS of 40-60. All patients went to the ICU postoperatively, and those requiring mechanical ventilation were sedated with propofol infusions titrated to the Richmond Agitation Sedation Scale (RASS) score of - 2 to + 1. Preoperatively, patients were screened via the MMSE, Hospital Anxiety and Depression Scale, and the Barthel Index. Delirium was assessed in the morning on postoperative days one through five with the CAM or CAM-ICU. The patient's RASS, pain, and sleep quality were also assessed.

On postoperative day six, MMSE was redone, secondary outcomes recorded, and on postoperative day 30, telephone interviews were done with the Chinese version of Telephone Interview for Cognitive Status (m-TICS). Li et al. (2017) found no significant difference between the two groups regarding the incidence of delirium during the first five days postoperatively (4.7% in the dexmedetomidine group and 7.7% in the control group). Mini- mental state examinations and m-TICS scores on postoperative day 30 were similar between the two groups. There were no significant differences in the overall incidence of non-delirium complications within 30 days and all-cause 30-day mortality. Pain intensity and subjective sleep quality were similar in both groups. However, in the dexmedetomidine group, the duration of mechanical ventilation was shorter and there were fewer pulmonary complications. As previously identified, anesthetic depth has been related to POD incidence. Because the BIS-guided anesthetic depth resulted in a lower BIS value in the dexmedetomidine group than in the control group, the results of POD incidence may be skewed. This study could have had more participants as there was a low incidence of delirium in the control group. Li et al. (2017) excluded patients with preexisting risk factors for delirium, preventing the generalizability of the results. This study found an increased incidence of hypotension in patients receiving dexmedetomidine, as did the metanalysis of noncardiac surgeries by Pan et al. (2019) and the metanalysis of both cardiac and noncardiac surgeries performed by Lin et al. (2021).

Shi et al. (2019) conducted a double-blinded, multiple center RCT of 64 elderly patients undergoing cardiac surgery with TIVA. The patients in the experimental group received 0.4-0.6 mcg/kg/hr of dexmedetomidine with remifentanil, propofol, and cisatracurium, whereas the control group received remifentanil, propofol, and cisatracurium, but did not receive dexmedetomidine. A Sedline brain function monitor that displays and processes four EEG waveforms and provides an index number like the BIS was used in all cases. The primary outcome was POD incidence within the first five postoperative days. The patients were assessed with the CAM twice daily, once in the morning and again in the evening. The Visual Assessment Scale (VAS), a pain measurement scale, was used to rate their pain. All patients received a morphine containing PCA postoperatively. The researchers collated the average morphine consumption and 24-hour VAS scores over the five postoperative days. A psychiatrist validated the delirium diagnosis. Shi et al. (2019) found no statistical difference in POD incidence between the two groups as POD occurred in 33 patients who received propofol only and 21 of the patients who received dexmedetomidine. The authors did find a decreased duration of delirium and observed a one-day, delayed onset of POD in the patients who received dexmedetomidine versus propofol. An important limitation of this study is the small population size and that no evaluations of the patient's preexisting mental state were included. It is essential to remember that inadequate analgesia contributes to POD incidence, as does morphine.

Likhvantsev et al. (2021) recognized the mixed findings of dexmedetomidine’s use on POD in cardiac surgery and conducted a single center, double blind, RCT in 169 patients over the age of 45 undergoing cardiac surgery on cardiopulmonary bypass. Patients in the experimental group received an infusion of dexmedetomidine at 0.7 mcg/kg/hr started on induction which was continued through the surgery into the postoperative period, where it was titrated to the patient's needs until mechanical ventilation was weaned. The control group received saline, but if patients in the control group required POD management in the ICU, the primary provider would be unblinded as the study's primary endpoint was reached, and propofol would be utilized. Sevoflurane was used as the general anesthetic in both groups. The CAM-ICU was used to assess patients for POD twice per day starting on postoperative day one through day five. The authors found a decreased incidence in POD in the dexmedetomidine group, six out of 84, versus the control, 16 out of 85 participants. There was no difference in the duration of POD between the groups. The severity of delirium was less in the dexmedetomidine group but only by one point on the Intensive Care Delirium Screening Checklist. Mechanical ventilation duration and duration in the ICU and the hospital were reduced in the dexmedetomidine group (Likhvantsev et al., 2021).

Halpin et al. (2020) performed a systematic review of 12 studies that were either RCT, observational or retrospective studies, or meta-analyses with at least one delirium assessment tool used. Eleven of the 12 studies had statistically significant evidence of decreased POD incidence with dexmedetomidine use. The original RCT conducted by Shi et al. (2019) was one of the studies included in this review and was identified as having a decreased POD incidence despite the original article deeming it was clinically insignificant as the difference in POD incidence was 12 participants. Halpin et al. (2020) recognized that the overall evidence indicated dexmedetomidine decreased POD in patients undergoing cardiac surgery but suggested that dexmedetomidine be used on a case-by-case basis until more evidence is collected in large, multi-center RCTs. This review included retrospective studies with larger populations but less control and prospective studies with smaller populations but higher control. Studies included a variety of independent variables. Two studies did not report how often delirium was assessed or who performed the assessment. Four studies did not definitively disclose the pain management strategy used. There is a lack of definitive dexmedetomidine administration timing in this review by Halpin et al. (2020), however, the included study titles reveal some perioperative and some postoperative use of dexmedetomidine. The reviewer can glean that postoperative use is encouraged per the authors' conclusion.

Wu et al. (2018) performed a systematic review and meta-analysis of 10 RCTs where 1387 participants aged 35-76 underwent cardiac surgery. These studies included the use of dexmedetomidine compared to saline or another drug, including midazolam, propofol, or remifentanil where the primary endpoint was POD. Three studies utilized dexmedetomidine intraoperatively into the postoperative period and six administered only dexmedetomidine postoperatively. This review found a generalized result of a significant (54%) decrease in POD incidence in the patients who received dexmedetomidine. Wu et al. (2018) urged early dexmedetomidine administration before or on arrival to the ICU for optimal delirium prevention.

Li et al. (2021) conducted a systematic review and metanalysis of 15 studies comprising 2,813 patients undergoing CABG or mixed CABG with valve replacement surgeries. Five of the studies included used dexmedetomidine intraoperatively whereas 10 started dexmedetomidine on chest closure and continued it through the duration of mechanical ventilation or at least for 24 hours after surgery. Overall results revealed specific conditions in which dexmedetomidine could reduce the risk of POD. Li et al. (2021) found postoperative dexmedetomidine administration in the adult population, but not in the aged population over the age of 65, decreased POD compared to other sedative medications but not when dexmedetomidine was compared to normal saline.

Administration Timing

Intraoperative

Of the 10 original studies included in this literature review that utilized intraoperative dexmedetomidine administration, seven showed a statistical difference in POD incidence. Of the three that did not, one was in noncardiac surgeries by Deiner et al. (2017) and two in cardiac surgeries (Li et al., 2017; Shi et al., 2019). Li et al. (2021) suggested the neurological insult from endothelial damage, blood brain barrier changes, cerebral blood flow changes, and microemboli from the use of the cardiopulmonary bypass may account for the increased POD incidence in cardiac surgical patients. These physiologic insults could be the reason that despite its neuroprotective and anti-inflammatory properties, dexmedetomidine was not effective in significantly decreasing POD in two original cardiac studies as well as two metanalyses in this literature review. Otherwise, the remainder of the original studies and systematic reviews and metanalyses revealed dexmedetomidine could decrease POD incidence.

Postoperative

Due to the search and inclusion criteria of the literature review, only systematic reviews and meta-analyses included studies that examined postoperative administration. Pan et al. (2019) reviewed 11 RCTs, three of which had postoperative dexmedetomidine administration. Qin et al. (2021) reviewed 13 RCTs, six of which administered dexmedetomidine both intraoperatively and postoperatively. The other seven were studies in which dexmedetomidine was administered intraoperatively; four are included in original studies in this literature review (Deiner et al., 2017; Lee et al., 2018; Li et al., 2020; Liu et al., 2016). Zeng et al. (2019) included six RCTs, and postoperative dexmedetomidine administration was the mode in two. These authors did not differentiate if the administration timing impacted the outcome of decreased incidence of POD with dexmedetomidine use.

Duan et al. (2018) examined 18 RCTs in which three included 2,180 patients who received dexmedetomidine postoperatively, three involved intraoperative use, and three examined its use both intraoperatively and postoperatively. Dexmedetomidine use exclusively in the intraoperative or postoperative period revealed a significant decrease in POD incidence but not when dexmedetomidine was used intraoperatively and postoperatively, which the authors referred to as the perioperative period. Ten of the 21 RCTs in the review by Lin et al. (2021) used dexmedetomidine postoperatively. Lin et al. (2021) also found that intraoperative and postoperative administration of dexmedetomidine resulted in decreased POD incidence but no difference was found when dexmedetomidine was administered both during and after the surgery, identified as perioperative use by the authors. Half of the 14 RCTs in cardiac and noncardiac surgeries reviewed and analyzed by Wang et al. (2021) observed a significant decrease in POD incidence when dexmedetomidine was administered postoperatively compared to intraoperative or perioperative use. This timing method and findings are in-line with the findings of Halpin et al. (2020), Li et al. (2021), and Deiner et al. (2017). In a meta-analysis and systematic review by Li et al. (2021) that included 15 RCTs where adults had undergone cardiac surgery: postoperative rather than intraoperative administration of dexmedetomidine had a significant effect in decreasing the incidence of POD and only had this effect in adults who were not elderly. Correspondingly, early administration of dexmedetomidine either at the end of the case or on arrival to ICU is recommended by Wu et al. (2018) in cardiac cases for optimal POD incidence reduction. Similarly, original research by Deiner et al. (2017) in patients undergoing noncardiac surgery urged consideration for dexmedetomidine administration timing to be focused postoperatively due to previous research revealing POD incidence decreased when dexmedetomidine was used in the postoperative period rather than propofol or benzodiazepines.

Studies Investigating POCD

Yang et al. (2019) explored the role of dexmedetomidine and inflammation in POCD in patients undergoing general anesthesia by systematically reviewing and meta-analyzing 26 RCTs in which dexmedetomidine or a placebo or comparable medication was administered either in a bolus or infusion before and during anesthesia. All but one of these studies took place in China utilizing the MMSE to assess patients for POCD. Of note, four of the RCTs did not report the age of the subjects and three studies included participants between the ages of 13 to 40 years. Surgery types included laparoscopic, general, orthopedic, cancer, lumbar, urologic, gynecological, and one surgery involving heart valves. The authors analyzed these studies according to POCD incidence reporting on postoperative days one, three, and seven, MMSE scores, inflammatory marker levels, and type of surgery. Yang et al. (2019) concluded that dexmedetomidine lowered the incidence of POCD in all major surgery types except for orthopedic surgery. In discussion, Yang et al. (2019) shared a study that showed inflammation in the hippocampus impacted memory in mice undergoing orthopedic surgery, supporting concerns about the insult that surgery inflicts with the inflammatory cascade. In this meta-analysis, these authors postulated that dexmedetomidine can decrease early POCD incidence and lessen the severity given higher MMSE scores found on postoperative day one. This meta-analysis found improved cognitive function via the MMSE scores in patients aged older than 60 who received dexmedetomidine with a 95% confidence interval and a standardized mean difference of 1.69. Lower TNF-α and IL-6, were measured in the dexmedetomidine versus the control group, solidifying dexmedetomidine's anti-inflammatory properties.

Zhou et al. (2016) performed a meta-analysis on 13 RCTs in patients undergoing general anesthesia for noncardiac surgery where dexmedetomidine was utilized either as a bolus or an infusion in the interventional group. The authors were interested in the POCD incidence and MMSE scores. Postoperative cognitive dysfunction was reported on the first postoperative day in 10 of the 13 studies and was reported thereafter in seven of the 13. The authors found a statistically significant decreased incidence of POCD in the dexmedetomidine group on postoperative day one, but not when reported after the first postoperative day. Mini-Mental State Exam scores were significantly higher on postoperative day one in the dexmedetomidine group than in the control group, consistent with findings by Yang et al., (2019). Zhou et al. (2016) concluded that dexmedetomidine can significantly decrease the early incidence of POCD and improve MMSE scores in the elderly patient undergoing surgery with general anesthesia.

Underlying Mild Cognitive Impairment

Three original studies included or specifically studied patients with baseline MCI. Liu et al. (2016) described MCI as a state where there is cognitive impairment, but memory is intact, suggesting MCI occurs as a potential shift between normal aging and Alzheimer's disease. Deiner et al. (2017) included patients with underlying MCI in addition to those without any known cognitive impairment, while Xin et al. (2020) looked at POD incidence in 60 adults with MCI undergoing laparoscopic cholecystectomy procedures. Liu et al. (2016) studied dexmedetomidine in the elderly with MCI undergoing knee replacements. Two out of these three studies found a positive outcome in intraoperative dexmedetomidine use to decrease POD occurrence in the elderly with preexisting cognitive impairment (Liu et al., 2016; Xin et al., 2021).

Liu et al. (2016) conducted a prospective, randomized, blinded, parallel-group study of 200 adults ages 65-80 years old with an American Society of Anesthesiologists (ASA) score of two or three. Eighty adults with baseline amnestic mild cognitive impairment (aMCI) and 120 elderly adult control patients undergoing total joint replacement were studied. Participants were randomly assigned to either aMCI dexmedetomidine or aMCI normal saline, a control group with dexmedetomidine, or a control group with normal saline. Before surgery, all patients received a neuropsychological assessment, and the CAM tool was used to screen patients for POD on postoperative days one, three, and seven. Participants in this study received TIVA with propofol and remifentanil because the authors cited the article that they published in 2013 indicating sevoflurane speeds up the progression of aMCI after two years. Zhang et al. (2018) identified via neuro marker levels that sevoflurane increases inflammation, and that the administration of dexmedetomidine decreased this inflammation, thus decreasing the risk of developing POD. In this study, Liu et al. (2016) found that older age in the aMCI group correlated to increased POD, whereas it did not in the control group, highlighting the risk factor of aging on POD development. POD incidence in the aMCI group was higher than in the control group. Importantly, dexmedetomidine did significantly decrease the incidence and duration of POD in the patients with aMCI at baseline.

The connection between POD, dexmedetomidine's neuroprotective properties, and neuroinflammatory markers was explored by Xin et al. (2021) in 60 patients with baseline MCI undergoing laparoscopic cholecystectomy. Patients were randomized to receive either dexmedetomidine or normal saline. A bolus of 0.5 mcg/kg of dexmedetomidine was administered over 10 minutes before induction, and an infusion at 0.4 mcg/kg/hr was continued until 30 minutes before the end of the case. A BIS goal of 40-60 was used, and medications were titrated based on hemodynamics. Blood samples were obtained before surgery, before suturing, and 30 minutes after surgery to measure the level of cytokines: TNF-α, IL-10, heme oxygenase-1 (HO-1), matric metalloproteinase (MMP-9), and glial fibrillary acidic protein (GFAP) in serum. Patients were assessed with the three-minute diagnostic interview CAM (3DCAM) tool twice per day for the first seven days after surgery. Blood level findings included elevated TNF-α, IL-10, MMP-9, and GFAP 30 minutes after surgery compared to those at baseline, indicating surgery increases inflammatory markers. The control group had higher levels of TNF-α, MMP-9, and GFAP and a lower level of IL-10 than the patients that received dexmedetomidine at the time of suturing and 30 minutes after the surgery. The authors pointed out this finding supported the belief that dexmedetomidine decreases neuroinflammation, and therefore decreases the risk of POD development. In this study there was a significant decrease in POD incidence in the patients who received dexmedetomidine. The incidence of POD was one-third in the control group and only one-tenth in the dexmedetomidine group.

Neuroinflammatory Markers

Dexmedetomidine modulates the inflammatory response inflicted by surgery, contributing to a decreased incidence of POD. Two original studies in the elderly receiving general anesthesia demonstrated this relationship. Zhang et al. (2018) conducted a RCT with 120 patients ages 65-75 with esophageal cancer who were randomly assigned to one of four groups: midazolam and propofol (M&P), midazolam and sevoflurane (M&S), dexmedetomidine and propofol (D&P), or dexmedetomidine and sevoflurane (D&S). Patients in the dexmedetomidine groups received a loading dose of 1mcg/kg followed by 0.5 mcg/kg/hr infusion. Propofol or sevoflurane was used to maintain anesthesia. Blood was collected 10 minutes before anesthesia, and on the first, third, and seventh postoperative days. Levels of IL-6, TNF-α, and S100 ß were measured. The MMSE and MoCA were used to assess the patients one day before surgery and on the first, third, and seventh postoperative days. Key findings of this study include a relationship between sevoflurane and increased POCD incidence as evidenced by significantly lower MMSE and MoCA scores in the midazolam and sevoflurane group compared to the midazolam and propofol group. In support of this relationship, plasma IL-6 and TNF-α concentrations were significantly higher in the M&S group than in the M&P group on postoperative days one, three, and seven. In addition, plasma S100 ß concentration was higher in the M&S group than in both the M&P group and the D&S group.

Furthermore, in the study conducted by Zhang et al. (2018), plasma IL-6 and TNF-α concentrations were the lowest in the dexmedetomidine and propofol group and highest in the midazolam and sevoflurane group at all monitored time points. This finding suggests sevoflurane released IL-6 and TNF-α but that dexmedetomidine inhibited this release. Additionally, MMSE and MoCA scores were higher on all three assessments in the dexmedetomidine and sevoflurane group than in the midazolam and sevoflurane group. The authors concluded that dexmedetomidine may be efficacious in decreasing the incidence of POCD caused by sevoflurane in the geriatric population. There was no significant difference between perioperative hemodynamics, time to recovery for spontaneous breathing, anesthesia emergence, or extubation time among the four groups (Zhang et al., 2018).

Lee et al. (2018) held a double-blind RCT in which 354 patients over 65 years of age undergoing laparoscopic major noncardiac surgery under general anesthesia received either a dexmedetomidine 1 mcg/kg bolus followed by 0.2–0.7 mcg/kg/hr infusion from anesthesia induction to the end of surgery (group D1), received a 1 mcg/kg bolus of dexmedetomidine 15 minutes before the end of surgery (group D2), or received only saline (group S). The CAM was used to assess patients preoperatively and at 12-hour intervals until postoperative day five. The primary outcome measure was the incidence of delirium for five days after surgery. Secondary outcomes included the duration of delirium for five days after surgery, and cortisol, C-reactive protein (CRP), and levels of cytokine TNF-α, IL-1β, IL-2, IL-6, IL-8, and IL-10 that were measured at one and 24 hours after surgery.

In this RCT by Lee et al. (2018) dexmedetomidine allowed for a decreased inflammatory response to surgery, impacting the incidence of POD. Group D1 had a decreased incidence, severity, and duration of delirium. Group D2 patients with delirium had a decreased duration compared with Group S. Duration of the delirium between group D1 and D2 was not significantly different. Patients with delirium in both group D1 and group D2 who received dexmedetomidine required less haloperidol than patients in group S. A lower level of IL-6 was noted at one and 24 hours postoperatively in group D1 than in group S. Plasma cortisol levels in groups D1 and D2 were lower than those in group S at one hour postoperatively. These neuromarker level results support dexmedetomidine's action as an anti-inflammatory agent, likely contributing to its effect on decreased POD incidence (Lee et al., 2018).

Hemodynamic Effects

Bradycardia and hypotension are the most common side effects of dexmedetomidine due to its action as an alpha-2 agonist causing vasodilation (Nagelhout &Elisha, 2018). Bradycardia was reported as a significant occurrence in nine RCTs investigated by Lin et al. (2021), three RCTs studied by Pan et al. (2019), three RCTs examined in Zeng et al. (2019), and six RCTs studied by Qin et al. (2021). Of note, several articles overlap that each systematic review and meta-analysis included. The cardiac surgery systematic review and meta-analysis done by Wu et al. (2018) observed significant bradycardia but not hypotension. Weerink et al. (2017) detailed that hypertension can initially be seen with dexmedetomidine administration as alpha-2 receptors in the vascular smooth muscles are affected, causing an increase in systematic vascular resistance via peripheral vasoconstriction. The baroreceptors are then responsible for the bradycardia seen. After the initial administration, the endothelial alpha-2 receptors are activated, causing vasodilation, and thus, hypotension. Hypotension is perpetuated by the decrease in catecholamines from dexmedetomidine's action at the presynaptic alpha-2 receptor (Weerink et al., 2017).

Li et al. (2021) discussed that dexmedetomidine's side effect of hypotension could be the reason why its use intraoperatively did not have a significant impact on POD reduction in the elderly population undergoing cardiac surgery. The authors emphasized the increased likelihood of the elderly to experience hypotension as well as the increased incidence of hypotension in cardiac surgery. Another consideration is the patient's preoperative exercise capacity, which is likely to be lower in the elderly population than in adults under the age of 65, leading to inability to tolerate the hypotension seen with intraoperative dexmedetomidine infusion. Postoperative dexmedetomidine use in the elderly after cardiac surgery did decrease POD in this systematic review and meta-analysis supporting the connection between hypotension and POD made by Li et al., 2021. Wu et al. (2018) suggested that an infusion of dexmedetomidine without a loading dose would allow for better hemodynamic profiles and still benefit the patient with the decreased incidence of POD.

Opioid Sparing Benefit

Pain and opioid use are known risk factors for the development of delirium (Li et al., 2020). Dexmedetomidine allows for decreased opioid consumption because of its action at the alpha-2 adrenergic receptor (Carr et al., 2018; Govêia et al., 2021; Pan et al., 2019; Shi et al. (2019). Analgesia is produced via dexmedetomidine's action at the alpha-2 site in the dorsal horn of the spinal cord, which decreases Substance P release (Govêia et al., 2021).

Impact on PONV

Patients who received dexmedetomidine as an intraoperative infusion in the original trial conducted by Li et al. (2020) had less early PONV than the control group who only received saline. A systematic review and meta-analysis of 14 RCTs by Wang et al. (2021) found that dexmedetomidine administration may decrease PONV incidence with a low level of evidence. Several authors make the potential connection that because dexmedetomidine can decrease opioid consumption, it can thereby decrease PONV (Weerink et al., 2017; Zeng et al., 2019). Dexmedetomidine also decreased the amount of volatile agent required to produce adequate anesthesia, which could explain this mechanism of decreased PONV seen with its use intraoperatively.

Length of Stay

In nine RCTs dexmedetomidine was found to decrease the length of stay in the ICU, and it was found to decrease the hospital length of stay in 11 of the 21 RCTs in the systematic review and meta-analysis of cardiac and noncardiac surgeries conducted by Lin et al. (2021). Hospital length of stay was not affected by dexmedetomidine use in the systematic reviews and metanalyses conducted by Wang et al. (2021) and Wu et al. (2018), however. The authors of the Duan et al. (2018) review, which included several of the same studies analyzed by Wang et al. (2021), did not find a high level of evidence in dexmedetomidine use impacting length of stay in either the ICU or the hospital. In their systematic review and meta-analysis, Pan et al. (2019) only examined noncardiac surgeries, which revealed a decrease in hospital length of stay when dexmedetomidine was used intraoperatively or postoperatively. In the original RCT held by Likhvantsev et al. (2021) in cardiac surgery patients, both the ICU and the hospital length of stay was decreased in the group that received dexmedetomidine. Overall, there is evidence in the literature that dexmedetomidine use could decrease both the length of stay in the ICU and the hospital.

Duration of POD

Overall, the use of dexmedetomidine has been shown to decrease the duration of POD. There are mixed findings in the literature, however. No difference in the POD duration was found in the original RCT in 169 patients undergoing cardiac surgery performed by Likhvantsev et al. (2021). Six of the 14 RCTs analyzed by Wang et al. (2021) reported that dexmedetomidine use decreased POD duration by a mean difference of 1.24 days. There was no significant difference in POD duration in the original study which included on pump cardiac, and major noncardiac surgeries conducted by van Norden et al. (2021). In the study by Lee et al. (2018), the duration of POD in the groups who received dexmedetomidine was shorter than the duration of POD in the group who received saline. However, there was not a significant difference in the duration of POD between the group who received dexmedetomidine in an infusion throughout the case and the group who only received a bolus of dexmedetomidine at the end of the case. This study proved that intraoperative dexmedetomidine use shortened the duration of POD.

Additionally, in the RCT of 64 elderly adults undergoing cardiac surgery, a decreased duration of delirium and a one-day, delayed onset of POD in the patients who received dexmedetomidine versus propofol was observed by Shi et al. (2019). Identical findings of decreased delirium and a one-day, delayed onset of POD were seen in a RCT by Liu et al. (2016) of patients with underlying symptoms of aMCI undergoing a total joint replacement. Duration of POD was not reported otherwise in the literature.

Mortality and Quality of Life

Mortality was assessed in several studies available in the literature. In eight of 14 RCTs, including cardiac and noncardiac surgeries, Wang et al. (2021) reported that dexmedetomidine use was associated with decreased mortality. A significant decrease in mortality was seen when dexmedetomidine was utilized in 10 out of 21 RCTs reviewed by Lin et al. (2021). At the three-month follow-up in the original trial including cardiac and major abdominal surgery held by van Norden et al. (2021), none of the patients who received dexmedetomidine had died, but five of the patients in the control group did. The patients' quality of life scores were similar in both groups at this three-month postoperative follow-up. Zeng et al. (2019) revealed that dexmedetomidine use had no significant effect on myocardial infarction or hypoxemia and did not significantly decrease all-cause mortality risk but decreased stroke incidence in three of the RCTs of noncardiac surgeries reviewed. Likhvantsev et al. (2021) found no difference in 30-day mortality or major adverse cardiac or cerebral events between the dexmedetomidine and control group in their original RCT in cardiac surgery patients.

Discussion of the Literature

Limitations in the Literature

Inclusion Criteria

The evidence was limited in large sample size, multiple-center studies with all-inclusive participant criteria. Many studies excluded patients with significant co-morbidities such as ASA physical statuses of four or five, those with end stage renal disease, Parkinson’s disease, any visual or hearing impairment at baseline, and those with a history of mental health diagnoses or traumatic brain injuries. As previously noted, three studies in this literature review examined the use of dexmedetomidine in patients with baseline cognitive impairment. This research is meaningful in its recommendations for the elderly population that is living longer and presenting for surgery.

Assessment and Monitoring

The question of consistency in POD assessment monitoring and the lack of follow up to determine long-term effects of POD are present throughout the literature. Liu et al. (2016) acknowledged the relationship between POD as a risk factor for POCD and recognized the importance of studying the long-term effects of POD on dementia and cognitive function. Systematic review and meta-analysis by Pan et al. (2019) revealed a lack of consistency in POD assessment timing. Several meta-analyses and RCTs revealed differences in monitoring frequencies throughout this literature review. Importantly, in the original study by Denier et al. (2017) that found intraoperative dexmedetomidine did not decrease POD, the authors only assessed patients for POD once a day and began the assessment in the PACU (Lin et al. 2021; Pan et al. 2019). The variations in assessment timing could have missed patients with signs of delirium. Meaningful assessment for POD utilizing the CAM tool twice per day starting on postoperative day one and conducted through until at least postoperative day five in the original trials by Lee et al. (2018), Li et al. (2020), van Norden et al. (2021), and Xin et al. (2020) lends strength to the outcomes and recommendations made in each of these studies.

Timing of Dexmedetomidine Administration

The optimal timing of dexmedetomidine for decreasing the incidence of POD was a theme throughout the literature. Original studies had some insight. Deiner et al. (2017) believed that postoperative administration made the difference as their study did not show intraoperative dexmedetomidine administration decreased POD incidence. Systematic review and meta-analysis by Li et al (2021) in patients undergoing cardiac surgery revealed postoperative but not intraoperative dexmedetomidine use decreased POD in the elderly population. Systematic reviews and meta-analyses by Duan et al. (2019) and Lin et al. (2021) revealed that intraoperative and postoperative dexmedetomidine administration decreased POD incidence. Lee et al. (2016) revealed that intraoperative administration was more effective than a one-time bolus or normal saline. Through a systematic review and meta-analysis, Pan et al. (2019) found that using a loading dose of dexmedetomidine did not significantly impact POD incidence outcomes. Govêia et al. (2021) concluded that the timing of dexmedetomidine administration did not matter as patients who received dexmedetomidine across 15 RCTs had a decreased incidence of POD compared to those who did not. This generalization is simple, generous, and has some merit. The decreased severity of POD outcome in patients who at least received a bolus of dexmedetomidine versus just saline in the original trial by Lee et al. (2016) aided this generalization made by Govêia et al. (2021), but the decreased incidence of POD in the group that received a bolus followed by a continuous infusion of dexmedetomidine supports the argument made by many studies suggesting calculated administration is optimal. Choosing the administration time is crucial when aiming to impact POD occurrence.

Future Research

The research is promising; there is sufficient data to suggest the use of dexmedetomidine in the aged population undergoing general anesthesia with both volatile agents and TIVA. More studies are on the horizon, including a single-center, double-blinded, placebo-controlled RCT proposed by Sui et al. (2021). With an aging population, the current evidence in the literature, the prevalence and consequence of delirium, it is necessary to continue examining dexmedetomidine use in aged patients undergoing general anesthesia.

Recommendations

In cardiac surgery, POD incidence is between 37 to 52% and is 5 to 51% in open abdominal surgery (van Norden et al., 2021). Practical strategies and evidence-based practice approaches for decreasing POD and POCD incidence are crucial as our population is aging. Overall, this literature review has revealed that intraoperative and postoperative use of dexmedetomidine decreased the incidence of POD and POCD when assessed via the CAM tool, decreased both the duration and severity of POD, improved cognitive functioning scores postoperatively, decreased opioid consumption, and decreased levels of inflammatory markers. Intraoperative and postoperative dexmedetomidine administration showed the most consistent results in terms of decreased POD incidence. A focus on prevention through preoperative optimization and the use of nonpharmacologic multicomponent approaches is currently a top treatment strategy for POD (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015; Oh et al., 2017; Vlisides &Avidan, 2019).

Conclusion

Due to the prevalence of POD and POCD, effective strategies to mitigate their development are merited in the elderly population undergoing general anesthesia. Postoperative delirium can cause increased hospital length of stay, increased morbidity and mortality, the decline of cognition and function, and high healthcare costs. Efforts should be focused on prevention rather than treatment due to the ineffective nature of decreasing the severity of duration once delirium has set in (Janssen et al., 2019). Many factors contribute to the development of delirium, including preexisting cognitive dysfunction, frailty, advanced age, malnutrition, polypharmacy, pain, hospital length of stay, and type of surgery (Janssen et al., 2019). Anesthetic depth, the inflammatory cascade, and hypotension have been suggested to impact POD development (Zhou et al. 2016). Strategies known to decrease the incidence of POD include the use of nonpharmacologic multicomponent interventions like the HELP, depth of anesthesia guidance with a BIS, and the use of dexmedetomidine. Further recommendations include assessing patients for risk factors to better hone on prevention as well as educating healthcare providers on assessments for early recognition and treatment to decrease duration and severity (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015; Oh et al., 2017; Vlisides &Avidan, 2019).

Of the 10 original studies, three did not find a statistically significant decrease in POD incidence when dexmedetomidine was administered to patients undergoing general anesthesia. Li et al. (2017) and Shi et al. (2019) assessed POD in patients undergoing cardiac surgery, whereas Deiner et al. (2017) conducted their trial in patients undergoing major noncardiac surgery. Of note, there was a small incidence of POD in general in the study by Deiner et al. (2017) and in the control group researched by Li et al. (2017), suggesting the potential for underpowered studies and potentially inaccurate results. Several authors point out a significantly short duration of dexmedetomidine administration in the landmark trial by Denier et al. (2017), where dexmedetomidine was administered on arrival to the OR through two hours postoperatively.

Of the 12 systematic reviews and meta-analyses included in this literature review, some of which examined outcomes in patients undergoing both cardiac and noncardiac surgeries and some only cardiac or noncardiac surgeries, all but two found that dexmedetomidine administration decreased POD incidence. Both Lin et al. (2021) and Wang et al. (2021) found an inadequate level of evidence that dexmedetomidine decreased POD in elderly patients undergoing cardiac surgery through their respective systematic reviews and meta-analyses. Some crossover of included studies was seen between the two author groups.

Attention to and the intention of anesthetic planning should focus on prevention and risk reduction, as anesthesia is a risk factor for POD development (Shi et al., 2019). With an aging population, anesthetic planning that considers POD and POCD reduction strategies are imperative. All the systematic reviews and meta-analyses agreed that dexmedetomidine administration in the elderly receiving general anesthesia decreased the incidence of POD in noncardiac surgery or could decrease the incidence of POD in cardiac surgery. Most of the literature revealed that intraoperative dexmedetomidine use decreased POD incidence in the aged population. Some of the literature recommended postoperative dexmedetomidine use to optimize decreased POD incidence. Dexmedetomidine use can improve patient outcomes with a reduction in POD and should be considered when planning an anesthetic in an aged patient.

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