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Influences of the Aging Process on Acute Perioperative Pain Management in Elderly and Cognitively Impaired Patients

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ABSTRACT

Background: The aging process results in physiological deterioration and compromise along with a reduction in the reserve capacity of the human body. Because of the reduced reserves of mammalian organ systems, perioperative stressors may result in compromise of physiologic function or clinical evidence of organ insult secondary to surgery and anesthesia. The purpose of this review is to present evidence-based indications and best practice techniques for perioperative pain management in elderly surgical patients.

Results: In addition to pain, cognitive dysfunction in elderly surgical patients is a common occurrence that can often be attenuated with appropriate drug therapy. Modalities for pain management must be synthesized with intraoperative anesthesia and the type of surgical intervention and not simply considered a separate entity.

Conclusions: Pain in elderly surgical patients continues to challenge physicians and healthcare providers. Current studies show improved surgical outcomes for geriatric patients who receive multimodal therapy for pain control.

INTRODUCTION

As the United States population ages, more surgeries are being performed annually in elderly patients, yet pain management continues to pose a challenge for clinicians. Studies and surveys of surgical patients have reported varying degrees and intensities of pain following surgery and inadequate postoperative pain management that sometimes necessitates hospital readmission.[1,2] Inadequate pain management can have profound and even long-lasting negative implications. Increasing evidence shows that uncontrolled or inadequately controlled pain after surgery is a risk factor for the development of chronic pain and that efforts to manage pain in the perioperative period may be effective in reducing the incidence of such an outcome.[3,4]

RAMIFICATIONS OF AGING AND INFLUENCES ON PERIOPERATIVE PAIN MANAGEMENT AND COGNITIVE DYSFUNCTION

Geriatric surgical patients have unique age-related changes in physiology and altered reactions to pharmacology. Many elderly patients have varying degrees of physical deconditioning (especially prior to lower extremity orthopedic procedures), poor perioperative health status, and compromised organ reserve capacity. In addition, age-related changes in the peripheral nervous system (PNS), the sympathetic nervous system (SNS), and the central nervous system (CNS) may affect functional outcomes during the perioperative period and should be considered in a patient's preoperative evaluation.

Peripheral Nervous System

Changes that occur in the somatic nervous system of the PNS with aging include (a) peripheral nerve deterioration, (b) dysfunction of genes responsible for myelin sheath protein components, (c) decreased myelinated nerve fiber conduction velocity, (d) mild motor and sensory discriminatory changes of the feet, and (e) changes of the senses (pain, touch, etc).

The autonomic division of the PNS also undergoes alterations secondary to aging. The autonomic nervous system (comprised of nerves, ganglia, and

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plexus) dictates most of the involuntary physiological functions of the body through parasympathetic and sympathetic divisions. The aging autonomic nervous system has reduced autonomic abilities that influence a patient's response to physiologic changes, stresses, surgery, pain, and anesthesia. Aging of the autonomic nervous system is characterized by (a) limited adaptability to stress, (b) net activation of the SNS, (c) decreased basal activity of the parasympathetic nervous system, (d) decreased baroreflex sensitivity, and (e) slowing and weakening of homeostatic functions—all of which may play a role in achieving good perioperative pain management. The autonomic nervous system and its effectors play an important role in responses to hemodynamic challenges, and advancing age can cause an imbalance of homeostatic mechanisms, resulting in orthostatic hypotension, exercise intolerance, increased upper body sweating, and temperature intolerance.

Sympathetic Nervous System

Increases in SNS activity are organ specific with the gastrointestinal system and skeletal muscle as targets. Neuronal noradrenergic reuptake is reduced in the elderly, resulting in an increased sympathetic tone of the heart and an increase in basal adrenal secretions along with attenuation of adrenal adrenergic secretion in response to stress and pain. There is a loss of beat-to-beat heart rate variability during respiration in the elderly due to reduced respiratory vagal modulation of the resting heart. Decreased baroreflex sensitivity is caused by increased arterial stiffness versus aging-associated alterations of the autonomic nervous system.

Central Nervous System

Normal aging results in biochemical and anatomical changes of the brain and spinal cord (Table 1). These changes include (a) volume of brain mass, number of synapses, and neurotransmitter concentrations; (b) cerebral electrical and metabolic activity; (c) changes in brain nerve fibers; (d) changes within the spinal cord (cervical spinal cord maintains its shape, but decreases in size); and (e) modification of the bony spinal canal (shape and area of spinal cord are independent of spinal canal diameter).

Brain sensitivity to anesthetic and analgesic agents increases with age and is unique to each drug. The mechanisms that define altered brain pharmacodynamics to anesthetics and analgesics in the elderly are unclear at the present, although altered brain kinetics may provide direction. Age-related altered brain sensitivity may result from changes in receptors, signal transduction, and homeostatic mechanisms of the CNS. Aging is associated with decreases in cholinergic and dopaminergic neurons and receptors, as well as decreased numbers of nervous system synapses. In addition, alterations of brain phospholipid chemistry associated with changes in second messengers, such as diacylglycerol, are evident.[5]

Memory deterioration occurs in >40% of people older than 60 years of age, and progressive loss of intellectual activity along with mental deterioration (senile dementia) occurs in 14% of the population aged ≥75.[6] Daily living activities can be dramatically affected by age-related memory decline. Memory decline is not inevitable, but deficiencies of specific neurotransmitters related to Parkinson disease, Alzheimer dementia, and other brain disorders often occur in geriatric patients. Changes in neurotransmitter activity and amounts have been implicated as factors influencing anesthetic agent sensitivity. Cerebral metabolic activity is decreased in older subjects and may be a result of decreased neurotransmitter concentrations and synaptic activity. Degenerative changes of myelin sheaths in the CNS may lead to cognitive dysfunction through changes in nerve conduction velocity that disrupt the normal timing of neuronal circuits. Another contribution to cognitive decline is the loss of cerebral white matter nerve fibers, resulting in decreased connections between neurons. Although these changes have been identified in the aging brain, the mechanism affecting functional activity reserve remains unclear.

The major signs, symptoms, and changes related to reductions of brain reserve in elderly patients include altered reflexes, deteriorations in gait and mobility, altered sleep patterns, impairment of memory and intellect, and decrements of the senses (vision, hearing, etc). Alterations of functional reserve in the elderly may manifest as increased susceptibility to postoperative cognitive dysfunction (POCD), delirium, altered pharmacodynamics, stroke, hyperalgesia, and sleep disturbances. Such reductions of brain reserve may predispose elderly patients to increased sensitivity to anesthetic and analgesic medications, symptoms and signs of perioperative neurologic dysfunction, increased risk of POCD, and a decrease in the functional activities of daily living. The various cognitive changes and dysfunctions that elderly surgical patients may experience are identified in Table 2.

Cognitive disorders can occur after surgery when mental function reaches a nadir in the early postoperative period and returns to preoperative levels within 1 week following surgery. CNS dysfunction is common in elderly postoperative patients, but stroke occurs relatively infrequently.[7] However, there are several risk factors for the development of cerebral

Table 1. Anatomical Changes of the Central and Peripheral Nervous Systems During Normal Aging

Central Nervous System	Peripheral Nervous System
1. Volume of thalamus and cortical gray matter decreases.	1. Number of large myelinated nerve fibers decreases and nerve fibers deteriorate (atrophy).
2. Volume of cerebrum, pons, corpus callosum, and cerebellum white matter remains intact (from ages 20-90).	2. Dysfunction of gene expression for protein components of the myelin sheath results in detrimental effects of remyelination.
3. Loss of neurons (neuronal cell death) in the cerebral cortex is limited (some neocortical areas lose no neurons).	3. Oligodendrocyte recruitment and differentiation are impaired.
4. Brain cells shrink and brain becomes more compact.	4. Sensory and motor functions of the feet are impaired.
5. Volume of intracranial cerebrospinal fluid increases (low pressure, nonpathological hydrocephalus).	5. Macrophage inflammatory responses are altered.
6. Regional reductions possibly occur in the neurotransmitters of serotonin, norepinephrine, dopamine, and acetylcholine.	6. The conduction velocity of myelinated nerves is decreased (unmyelinated fibers unaffected by aging).
7. Cerebral blood flow, cerebral metabolic activity, and O2 consumption decrease.	7. Changes occur in pain sensitivity, as well as in the senses of touch, taste, hearing, and sight; smell is not affected.
8. Degenerative changes occur in myelin sheaths of nerve fibers.	8. Adaptability to stresses is limited.
9. Nerve fibers from the cerebral white matter are lost.	9. Reduced noradrenergic reuptake yields a net activation of the sympathetic nervous system.
10. Reactive gliosis and neuronal loss occur in the spinal cord.	10. Dysfunction of homeostatic functions manifests in heat intolerance, orthostatic hypotension, and intolerance to exercise.
11. Loss of cell bodies and shrinkage/degeneration of nerve fibers occur in dorsal columns of cervical spine, ventral horn, and gray matter (intermediate) of spinal cord thoracic segments.	11. If the autonomic nervous system is attenuated, perioperative lability of hemodynamics may be suspected.
12. The cephalic extremity of the spinal cord atrophies; anterior-posterior diameter and transverse area of the cervical spinal cord decrease.	12. Activity of parasympathetic system decreases.
13. The bony spinal canal narrows.	

vascular dysfunction (perioperative stroke), and stroke is a leading cause of death and permanent disability because of the resulting functional impairments in the older surgical patient.[8]

One important risk factor to consider in elderly patients is evidence of clinical depression. Depression is associated with a significantly increased risk of stroke.[9] In addition, depression after stroke can affect the likelihood of functional recovery and positive long-term outcomes.[10] This evidence is a good indication for continuing antidepressive medications in older patients throughout the perioperative process.

Postoperative delirium (POD) and POCD are common complications in elderly surgical patients

Table 2. Cognitive Impairment Definitions

Mild Cognitive Impairment (MCI)	1. This concept describes a transitional level of neurocognitive impairment. 2. MCI is a predictor of future dementia. 3. Diagnosis is by neuropsychological testing and clinical observation. 4. Four subtypes are associated with causes of dementia. Subtypes are based on the presence of memory impairment plus the number of other cognitive domains affected. 5. Preoperative MCI may result in postoperative delirium.
Delirium	1. Fluctuating consciousness develops in hours to days. 2. Characteristics are altered perception and cognition not associated with dementia. 3. In-hospital predictors of delirium include the following: - bladder catheters - malnutrition - 3 or more medications - iatrogenic events - alcohol and drug abuse - decreased functional status - infection - H2 antagonists - benzodiazepines - male gender - depression - age - opioids
Postoperative Delirium (POD)	1. POD develops on postoperative day 1-3 and can be sustained $>$1 week. 2. Age-associated central cholinergic deficiency is a positive predictor. 3. The 2 types of postoperative delirium are - hypoactive (more common and more commonly overlooked) - hyperactive 4. Perioperative use of benzodiazepines is associated with POD. 5. Postoperative in-dwelling perineural catheters reduce the incidence of POD.
Emergence Delirium	1. Emergence delirium may be present upon regaining consciousness following general anesthesia. 2. Emergent delirium predicts postoperative delirium.
Postoperative Cognitive Dysfunction (POCD)	1. Patients have difficulty performing cognitive tasks after surgery that they could perform prior to surgery. 2. POCD occurs frequently following carotid endarterectomy, hip fracture repair surgery, and cardiac surgery (most frequent). 3. International Study of Postoperative Cognitive Dysfunction developed criteria for POCD based on pre- and postoperative neuropsychological testing scores. 4. Predictors of POCD 1 week postoperatively include the following: - duration of anesthesia - postoperative infection - pulmonary complications - age (predictor of POCD at 3 months) - low level of patient education - need for a second operation
Dementia	1. Alzheimer disease is the most common form; other types are vascular, frontal lobe, reversible, senile, Lewy body, and Parkinson-associated dementias. 2. Apathy and personality changes occur early. 3. Behavioral changes appear as the condition progresses. 4. Psychotic symptoms are late signs (typically difficult to control). 5. Condition is characterized by multiple cognitive deficits. 6. Clinical findings are associated with the following: - problems with social activities - decline from a previous status - problems of occupational activities 7. Gradual and progressive loss of mental abilities occurs. 8. Patients with dementia often have postoperative delirium.

and have a higher incidence than other postoperative comorbidities such as respiratory failure and myocardial infarction.[11] The incidence of POD and POCD may exceed 50% in certain surgical settings such as cardiac and orthopedic (femoral neck fracture repairs) surgeries,[12,13] creating issues as to how to best treat surgical pain that cannot be properly assessed. Complications of POD and POCD are significant because such adverse outcomes can result in increased length of hospital stay, medical complications including death, and unmet postoperative analgesic needs. In addition, patients with POD or POCD often require discharge to skilled care facilities.[14,15] The economic impact of delirium is considerable, adding costs to hospitalizations and billions in additional Medicare charges.[16]

Geriatric patients undergoing certain high-risk types of surgery and patients with certain coexisting medical diseases, preoperative cognitive dysfunction, and advanced age are at higher risk for developing postoperative cognitive disorders and long-term cognitive dysfunction that further complicate postoperative pain management scenarios. Research indicates that cognitive disorders in high-risk elderly patients occur more frequently than anticipated. In one study, 25.8% of patients (n=1,200) older than 60 years had an incidence of cognition impairment postoperatively at week 1 that persisted in 9.9% of patients until 3 months following surgery.[17] Results from this study show that cognitive dysfunction can be common in adult patients of all ages at hospital discharge after major noncardiac surgery, but only the elderly (60 years and older) are at significant risk for long-term cognitive problems. In addition, the study indicates that patients with POCD are at an increased risk of death during the first year after surgery.

Therefore, perioperative pain management strategies capable of reducing or eliminating potential triggers (nonopioid analgesics, regional techniques, etc) for cognitive dysfunction, POD, and POCD may prove beneficial in older surgical patients. The challenge for healthcare providers is to investigate whether anesthetic/analgesic options, other than opioids for example, exist that will provide efficacious perioperative pain management and reduce morbidity/mortality for at-risk elderly patients.

The functional status of elderly surgical patients may be more relevant than medical morbidity outcomes. Cognitive status relates directly to the patient's functional ability—a determining factor in rehabilitation, pain management, and whether or not a patient is discharged to home or will require a skilled care facility for recovery. In addition, functional status serves as a strong predictor of mortality resulting from hospitalization.[18] Impaired neurocognitive function decreases the patient's health-related quality of life and has adverse financial and social impacts on patients and their care providers. Finally, postoperative cognitive dysfunction can serve as a marker for the quality of hospital care.[19]

IMPLICATIONS OF COEXISTING DISEASE

While age-related changes can have a significant effect on outcomes, patient age alone is not the only risk factor predictive of anesthesia and surgery risks. Complication rates of both anesthetic and perioperative pain management choices increase very little with advancing age in absence of coexisting disease.[20,21] The number and extent of coexisting diseases and medical conditions are more directly related to elderly patient perioperative risk than chronological age. Better predictors than age are overall physical status, medical history, disease state or condition, and type of surgery. Adverse medical conditions that indicate the need for concern and predict higher surgical risk are diabetes mellitus, hypertension, and ischemic heart disease.[22]

Therefore, geriatric patients may be at increased risk of perioperative morbidity and mortality because of their coexisting disease (four-fifths of older patients have at least 1 complicating condition and one-third have 3 or more coexisting diseases),[23] but additional issues of concern for the elderly remain the type, urgency, and potential duration of surgery—all of which are important predictors of patient outcome and perioperative risk management.

PAIN AND DRUG THERAPY

Aside from ophthalmologic procedures, the most routinely performed surgical interventions are orthopedic and general surgeries.[24] Upper abdominal surgical procedures followed by thoracic and open-heart surgical procedures are associated with the highest morbidity and mortality and pose an increased risk for elderly surgical patients' perioperative pain management. Common perioperative morbidity complications of the elderly include neurologic, pulmonary, and cardiovascular problems.

Acute pain is an expectation in hospitalized elderly patients, especially in postoperative patients. Perioperative pain has become a significant therapeutic concern for many practitioners, and the associated costs of treatment have made it a public health concern. Because surgical patients rarely present with pure nociceptive or neuropathic pain, but rather with mixed postoperative pain management needs, a rational and polypharmacy (ie, multimodal) approach targeting key peripheral and central pain mechanisms and modulating pathways often yields acceptable outcomes.

During the previous decade, the multimodal drug therapy approach has gained value and utility as an effective strategy for pain management.[25] By using different analgesic drug classes, each targeting different receptors and pathways, multimodal analgesia can optimize analgesic efficacy and provide the ability to use lower medication doses of each agent with an emphasis on limiting adverse events (AEs) and risks associated with dependence and dose-related consequences of opioids alone and/or single nonopioid analgesic drug adjuncts. Clinicians often find this pain management approach beneficial, especially when they are able to use regimens that rely less on opioid drugs.

Using opioids as the central or major agent for perioperative pain management in the elderly carries a host of well-known AEs.[26] Opioids have been linked to disturbed sleep architecture (reduced rapid eye movement and slow wave sleep) that can result in sleep deterioration that causes hyperalgesia, worsening sleep even more and leading to a vicious cycle.[27] Also, both adenosine and acetylcholine levels decrease after opioid administration, and levels of these neurotransmitters in the basal forebrain are major players in regulating centrally perceived pain (in addition to memory, attention, and wakefulness). The elderly are particularly sensitive to reductions in these levels, and their baseline reserves are typically reduced.

In addition, reliance on only parenteral opioids for the elderly after major surgery has been shown to cause profound delays in gastric absorption that may have implications regarding most optimal route of medication delivery in the perioperative period.[28] Consequently, opioid monotherapy alone may result in inadequate postoperative pain management because of the associated and varied common AEs that limit these drugs' utility in the elderly surgical patient.

Medication combinations with the potency to modulate one or more discrete pain transmission mechanisms have favorable safety profiles in the elderly and proven advantages.[29] Analgesic medications given intravenously can enhance bioavailability and have an earlier onset of effect during the perioperative period. Therefore, the multimodal analgesic paradigm—including fast onset of action, proven safety profiles, reductions in pain, delivery by multiple routes, and reduced AEs—has been shown to be efficacious in multiple studies and may also improve outcomes by reducing the opioid amounts required for optimal pain control for a wide variety of surgical interventions.[24,25,30]

REGIONAL ANESTHESIA

Various anesthesia and analgesia techniques are available (Table 3). Investigations of regional anesthesia (RA) include different drug regimens and regional techniques and include the following: RA versus combined RA and general anesthesia (GA), RA only versus combined RA and regional analgesia, and thoracic versus lumbar neuraxial anesthesia/analgesia.[31-35] Lack of consistency in RA studies and protocols has inhibited the ability to determine firm indications and recommendations about advantageous or optimal anesthetic/analgesic techniques for particular surgical interventions in the geriatric population.

Perioperative clinical outcomes associated with RA effectiveness, morbidity (traditional and nontraditional complications)[33] and mortality include pain management; economic impact; functional health status; quality of life measurements; and effects on cognition, coagulation, the CNS, and the cardiovascular, pulmonary, gastrointestinal (GI), immune, and endocrine systems. Therefore, it is important to consider patient age, anticipated surgical procedure, patient comorbidities, and potential postoperative pain management requirements before deciding upon an anesthetic technique and perioperative pain management strategy for the elderly patient.

RA and continuous analgesia (either neuraxial or peripheral regional) delivery systems can provide targeted pain relief and can minimize the amount of systemic opioids administered in the perioperative period, consequently reducing the many AEs associated with opioids. Optimal postoperative analgesia and analgesic effects (superior physiologic benefits and minimal negative consequences) may be improved by placing RA in proximity to the corresponding dermatome distribution of the surgical site[36-40] or by using multimodal medication therapy, permitting less reliance on opioid analgesics in the elderly surgical patient.

Neuraxial anesthesia, along with peripheral nerve and nerve plexus blockade as a component of multimodal analgesia, may enhance recovery and reduce reliance on standard therapy from opioids in older surgical patients. However, further study needs to be conducted to identify the most appropriate pain management techniques for commonly performed surgical procedures and for patient comorbidities (including age). For example, could RA and analgesia become procedure-specific for older patients and what are the technique-specific regional modalities of pain management in elderly patients who have particular comorbid diseases?

The choice of analgesic agents used with RA (local anesthetics with or without opioids and other adjuncts) will influence patient outcome. Central neuraxial opioids are effective in controlling postop-

Table 3. Analgesia and Anesthesia Techniques

Type	Description
Local Monitored Anesthesia Care (LMAC)	With or without intravenous and oral sedatives, hypnotics, and analgesics (opioid and nonopioid)
General Anesthesia and Analgesia	With or without perioperative medications
Anesthesia	Inhalation agents, intravenous agents, and/or total intravenous
Analgesia	Opioids, nonopioids, and other adjuncts administered via the following methods: - intramuscular injections - intravenous boluses - patient-controlled analgesia - transdermal, mucous membrane, and oral routes
Regional Anesthesia and Analgesia	With or without other intravenous perioperative medications (analgesics, sedation)
Neuraxial	Spinal (subarachnoid) and/or epidural anesthesia and/or analgesia delivered via single injection with or without catheters Local anesthetic (type, concentration) with or without opioids and other adjuncts
Peripheral Nerve/Nerve Plexus Blockade	Local anesthetic with or without additives delivered via single injection or continuous catheter technique
Infiltration/Field Block	Local anesthetic infiltration/injection (diffusion blockade) with or without indwelling catheters

erative pain, but only epidural local anesthetics have shown the ability to attenuate the adverse pathophysiological responses that can contribute to perioperative morbidity.[41] Neuraxial local anesthetics are effective through their prevention of spinal reflex inhibition of diaphragmatic and gastrointestinal function, suppression of responses to surgical stress, and blockade of efferent and afferent nerve signals to and from the spinal cord. Epidural local analgesia used without neuraxial opioids may improve patient outcomes by decreasing the incidence of respiratory complications and promoting the earlier recovery of gastrointestinal motility following abdominal surgery.[42,43] Perioperative RA techniques in the elderly influence and control perioperative pathophysiologic events by (a) reducing neuroendocrine stress response, (b) improving effective pain control, (c) facilitating the return of gastrointestinal function (earlier enteral feeding), and (d) resulting in earlier patient mobilization, as well as playing an integral role in the management of recuperating patients.[44]

Several studies have shown that perioperative RA as part of a multimodal paradigm during the convalescence of elderly surgical patients improved patient outcome, ameliorated many negative pathophysiologic events, and provided improved analgesia. Brodner et al showed that postoperative RA as part of a perioperative multimodal approach in patients undergoing abdominal-thoracic esophagectomy resulted in a shorter time to patient extubation, earlier return of bowel function, superior analgesia, and earlier fulfillment of discharge criteria from an intensive care unit.[45] In another Brodner et al study, patients receiving perioperative multimodal therapy following major surgery had a decrease in metabolic and hormonal stress along with improvement in convalescence.[46] Basse and colleagues showed that patients undergoing colon resection who received epidural analgesia and a multimodal approach to surgical rehabilitation had a decreased length of hospitalization from 6-10 days to a median of 2 days.[47] A review conducted by Kehlet and Wilmore showed that incorporating perioperative RA techniques and utilizing a multimodal anesthetic approach to surgical rehabilitation attenuated pathophysiological surgical responses, reduced the length of hospitalization, and resulted in accelerated patient recovery for the elderly.[48]

While central neuraxial blockade has many potential benefits, the incidence of neurologic compromise resulting from hemorrhagic complications associated with this RA modality (spinal, epidural, etc.) is not completely known. Although the incidence cited in the literature is estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics, recent epidemiologic surveys suggest that the frequency is increasing and may be as high as 1 in 3,000 in some patient populations (such as patients with varying degrees of coagulopathy, both clinical and subclinical).[49,50] The risk of clinically significant bleeding increases with advanced age, abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during neuraxial needle placement, and presence of an indwelling neuraxial catheter during sustained anticoagulation (particularly with standard heparin or low-molecular weight heparin).

In response to these patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Third Consensus Conference on Regional Anesthesia and Anticoagulation and developed practice guidelines that summarize evidence-based reviews.[49] The rarity of neuraxial hematoma defies a prospective randomized study, and because no current laboratory models exist on which to base clinical decisionmaking, the ASRA consensus statements represent the collective experience of recognized experts in the field of neuraxial anesthesia/analgesia and anticoagulation. A fund of knowledge is based on clinical series, pharmacology, case reports, hematology literature, and risk factors for surgical bleeding, but evidence-based outcomes are currently not available. An abbreviated version of the ASRA consensus conference parameters on neuraxial blockade and perioperative coagulation is provided in Table 4, but an understanding of the complexity of this issue is essential to optimal patient perioperative anesthetic/analgesic management.

REGIONAL ANESTHESIA EFFECTS ON SYSTEMS IN THE ELDERLY

Cardiovascular System

A variety of morphological and functional changes of the cardiovascular system occur with aging (Table 5). These aging effects have important clinical implications for the treatment of elderly surgical patients and their postoperative pain management, especially for patients receiving RA. Currently, there is little evidence to suggest differences in cardiovascular outcome, morbidity, and mortality using RA or multimodal drug therapy in the elderly,[35,51] although studies have shown a significant benefit and influence on short-term survival with RA.[37,52-54] For example, when epidural anesthesia and analgesia are combined with GA for elective abdominal aortic aneurysm repair, a shorter duration of postoperative intubation is required, time within and resources of the intensive care unit are reduced, incidence of death and major complications is decreased, postoperative pain relief is better, and overall outcome is improved.[52] In addition, early placement of continuous epidural analgesia in elderly patients who have had hip fracture surgery versus a regimen of systemic opioids has been associated with a reduced incidence of adverse cardiac events.[53] Thoracic epidural analgesia may attenuate adverse cardiovascular pathophysiological events because epidural analgesia decreases cardiac sympathetic outflow, yielding a more favorable balance between myocardial supply and demand. Statistically proven beneficial influences from RA on the incidence of myocardial ischemia, myocardial infarction, or myocardial malignant arrhythmias have not been shown; however, the use of thoracic epidural analgesia (not lumbar) has revealed a statically significant reduction in ventricular malignant arrhythmias and a decreased incidence of postoperative myocardial infarction.[37]

A recent metaanalysis of randomly controlled trials ($n=9{,}559$) showed that patients undergoing various orthopedic procedures and receiving neuraxial blockade had a one-third reduction in overall mortality.[55] Another metaanalysis ($n=2{,}427$) found that patients who received epidural anesthesia and analgesia (with or without GA) had a reduced incidence of perioperative myocardial infarction, and when a thoracic epidural was maintained for analgesia longer than 24 hours, results showed significantly fewer postoperative myocardial infarctions.[37,54] Yet another metaanalysis ($n=68{,}723$) of Medicare patients found a significantly lower odds ratio of death at 7 and 30 days when postoperative epidural analgesia was used.[56]

Perioperative stresses of lifestyle disruption, anesthesia, surgery, postoperative pain, and convalescence will activate (to varying degree) the SNS of an elderly surgical patient with mixed and potentially negative imbalances between myocardial oxygen supply and demand, predisposing the patient to myocardial ischemia and infarction. Perioperative myocardial infarction and other deleterious cardiovascular events such as congestive heart failure, sudden death, and cardiac arrhythmias typically occur with increased frequency within the first few days following a major surgical intervention.[38,57] Another important factor to consider in geriatric surgical candidates that can influence development of perioperative myocardial ischemia and infarction is the negative contribution from hypercoagulation during the surgical perioperative period.[58]

Table 4. Abbreviated Version of American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines for Anticoagulation and Regional Anesthesia[49]

Drug	Recommendations for Neuraxial Anesthesia/Analgesia	Comments
Unfractionated Subcutaneous Heparin (UFH)	5,000 U BID used alone has NO contraindication to neuraxial block >BID or >10,000 U/daily: insufficient data, therefore, decision based on risk-to-benefit. TID UFH should be assessed on an individual basis + enhanced neurologic monitoring UFH >4 days: assess platelet count prior to neuraxial catheter removal	>bleeding risk with TID dose (>10,000 U/day) AVOID neuraxial catheter during TID dosing TID dosing + neuraxial catheter: enhance neurologic monitoring and use neuraxial medications that permit neurologic monitoring
Unfractionated Intravenous Heparin	Assess coagulation, contraindicated with other coagulopathy Postoperative neurologic monitoring MUST be performed (at least 12 hours) and consider postoperative neuraxial solutions that permit neurologic monitoring Assess risk-benefit with bloody or difficult neuraxial block (do NOT have to cancel surgery—communicate with surgical team) Delay IV heparin ≥1 hour after neuraxial needle placement Remove neuraxial catheter 2-4 hours after last dose and delay restarting heparin for 1 hour after removal while assessing coagulation status STOP heparin infusion 2-4 hours prior to neuraxial catheter removal Contraindicated in combination with other coagulopathy or other anticoagulants	Neuraxial techniques with intraoperative IV heparin is acceptable; however, caveats do exist Insufficient data to assess risk with therapeutic anticoagulation—close postoperative neurologic monitoring + neuraxial solutions that permit neurologic monitoring Greater bleeding risk with therapeutic IV heparin in the presence of neuraxial catheter 5,000-10,000 U IV heparin is NOT systemic heparinization
Low Molecular Weight Heparin (LMWH)	Evidence of blood/traumatic neuraxial blockade: first LMWH delayed for 24 hours Preoperative LMWH: prophylaxis-neuraxial needle placement 10-12 hours after last LMWH Preoperative LMWH: therapeutic-neuraxial needle placement 24 hours after last LMWH Preoperative LMWH: within 10 hours of surgery-NO neuraxial techniques Postoperative LMWH and neuraxial block: QD dose 6-8 hours postoperative, second dose 24 hours after first, neuraxial catheter OK, catheter removal 10-12 hours after last LMWH and next dose >2 hours following catheter removal Postoperative LMWH and neuraxial block: BID dose 24 hours postoperative, neuraxial catheter NOT OK, first dose >2 hours after neuraxial catheter removal	Potentiation with other medications with anticoagulant effect NO value in routine testing for anti-Xa levels and NO reliable monitoring to LMWH therapy LMWH is IRREVERSIBLE with protamine Increased risk of neuraxial hematoma: immediate pre- or intraoperative dosing, BID dosing, early postoperative dosing, other concomitant anticoagulants

Table 4. Continued

Drug	Recommendations for Neuraxial Anesthesia/Analgesia	Comments
Warfarin	NO neuraxial blockade during uninterrupted warfarin therapy STOP warfarin 4-5 days prior and confirm normal INR before neuraxial techniques; if dose given $\geq$24 hours prior or second dose given, then check INR before neuraxial blockade Low-dose therapy + neuraxial catheter = continuous/daily INR monitoring Neuraxial catheter removal = INR <1.5 and continue neurologic assessment for 24 hours (INR $\geq$1.5 = catheter removal with caution and continue neurologic monitoring) INR $\geq$3 + neuraxial catheter = hold warfarin or reduce dose	Avoid concomitant anticoagulant drugs Neurologic monitoring and use neuraxial medications that permit neurologic monitoring in conjunction with low-dose therapy INR NOT reliable indicator of all factor levels
Antiplatelet Drugs (thienopyridine derivatives, NSAIDs, platelet glycoprotein IIb/IIIa inhibitors)	NO neuraxial blockade if NSAIDs and concomitant anticoagulant drugs Thienopyridines: clopidogrel-STOP 7 days prior and ticlopidine-STOP 14 days prior to neuraxial blockade Platelet glycoprotein IIb/IIIa inhibitors: NO neuraxial technique until platelet function recovery Tirofiban - 4-8 hours Eptifibatide - 4-8 hours Abcixmab - 24-48 hours	Aspirin or NSAIDs ALONE = NO contraindication to neuraxial techniques Bleeding time is NOT an indicator of platelet function Aspirin inhibits platelet function for life of platelets, and NSAIDs affect platelets 3 days after last dose COX2 inhibitors–probably NO platelet dysfunction
Fondaparinux	Atraumatic single needle pass and AVOID neuraxial catheter placement First dose >2 hours following neuraxial catheter removal	Factor Xa inhibition has 21-hour half-life
Thrombin Inhibitors (bivalirudin, desirudin, etc)	Contraindication to neuraxial techniques	For patients needing therapeutic anticoagulation with history of heparin-induced thrombocytopenia
Herbal Medications (garlic, ginseng, etc)	Herbal drugs alone do NOT contraindicate neuraxial techniques	Herbal medications alone do NOT increase risk of neuraxial bleeding
Direct Thrombin and Activated Factor Xa Inhibitors	Prolonged half-life warrants EXTREME caution with neuraxial techniques Risk vs benefit prior to neuraxial blockade	Examples: dabigatran, rivaroxaban Lack of data to determine safety profile in combination with neuraxial techniques

BID, twice daily; INR, International Normalized Ratio; IV, intravenous; NSAIDS, nonsteroidal antiinflammatory drugs; QD, once daily; TID, 3 times daily; U, units.

Notes: Anticoagulation and Neuraxial Anesthesia/Analgesia

1. Neuraxial (spinal/epidural) anesthesia and analgesia in combination with different anticoagulants and anticoagulation regimens require special consideration.
2. Risk of hematoma formation and benefit of neuraxial blockade must be considered when performing neuraxial techniques and/or neuraxial catheter placement and removal in combination with prophylactic and/or therapeutic anticoagulation.
3. Coagulation status should be normalized during neuraxial blockade placement.
4. Anticoagulation levels MUST be monitored while neuraxial catheters are present.
5. Neuraxial catheters MUST NOT be removed during therapeutic anticoagulation.
6. Diagnostic imaging and surgical therapy protocols for early treatment of neuraxial hematoma neurologic symptoms MUST be followed.

Table 5. Influence of Aging on the Cardiovascular System

Morphological Changes	Functional Effects
Progressive loss of elasticity of large arteries Generalized hypertrophy of the left ventricular wall	Increased systolic blood pressure Increased afterload for the left ventricle Increased left ventricular end-diastolic volume
Fibrotic changes and diminished elasticity of heart muscle (reduced myocardial compliance)	Volume-sensitive and volume-intolerant cardiovascular system
Reduced compliance of LVEF	Inability to optimally respond to stress (cannot significantly increase LVEF)
Cardiac output maintained by increasing end-diastolic volume	Increased stroke volume
Elderly patients may not maintain blood pressure when challenged with minor hypovolemia or added cardiovascular stresses	
Sympathetic blockade from neuraxial anesthesia may lead to hypotension in a setting of hypovolemia	

LVEF, left ventricular ejection fraction.

Respiratory System

The perioperative risk of surgery among elderly patients that is attributable to respiratory complications—regardless of anesthetic/analgesic modalities used—is explained by the functional and structural changes within the pulmonary system (Table 6). For instance, age-related decreased respiratory muscle strength becomes relevant under stresses of left ventricular failure or pneumonia, elderly patients are less able to adequately meet respiratory demands induced by hypoxia and hypercarbia, a greater decrease in arterial oxygen tension is needed to increase minute ventilation, and the elderly may not increase their minute ventilation under stress of illness or injury with the increased production of carbon dioxide.[59] Consequently, clinicians should titrate analgesic medications carefully and assess patients frequently for evidence of AEs and adequate pain control. The use of neuraxial and peripheral nerve/nerve plexus blockade appropriately matched to procedure-specific surgery may minimize adverse respiratory effects that could be further exacerbated by more conventional anesthetic/analgesic approaches (general anesthesia, opioids, etc). For example, epidural analgesic techniques may benefit elderly patients undergoing thoracic and upper abdominal surgery because these techniques allow quick restoration of respiratory function and have the added benefits of decreased morbidity, hospital stay, and healthcare costs.[60]

Many studies have shown that the anesthetic/analgesic choice has no significant long-term effect on perioperative respiratory morbidity and mortality within any age group.[61-63] However, it is reasonable to conclude that elderly patients may benefit from RA because they can remain minimally sedated (preserving pulmonary function), airway manipulation is avoided, postoperative pain control is provided, and recovery from adverse respiratory influences may be minimized or reduced through the elimination of inhalation anesthetics/GA. Therefore, the decision to perform RA must be determined on a case-by-case basis considering the patient's pulmonary function, health status, and anesthesiologist expertise, along with the type and duration of the planned surgery.

Vital capacity (VC) can be reduced in patients with upper abdominal incisions (25%-50%) who receive systemic opioid analgesics that contribute to alteration/reduction in tidal volume and impair the clearing of secretions (altered cough mechanics).[42] Reduced functional residual capacity (FRC) is associated with ventilation-perfusion (V/Q) mismatching, increased alveolar-to-arterial oxygen gradient, and decreased efficiency of gas exchange. Further reductions in FRC are created when patients assume the supine position and are under the influence of GA. GA can reduce FRC by 15%-20%, and the reduction can last 7-10 days after surgery.[64] Older patients undergoing GA are predisposed to atelectasis from the combination of reduced FRC and age-associated increases in closing volume. Unchanged FRC, from baseline, has been observed during spinal and lumbar epidural anesthesia. However, intercostal blocks and cervical or high thoracic epidural blockade can be associated with lung volume reduction secondary to intercostal muscle relaxation. Therefore, the choice of anesthesia/analgesia may affect the patient's degree of pulmonary dysfunction. Studies have shown that elderly patients undergoing lower extremity orthopedic procedures have fewer hypoxic events with epidural anesthesia (using local anesthetics) compared to systemic opioids; GA in older patients results in lower PaO2 levels (on postoperative day 1) compared to epidural anesthesia; and respiratory complications are less frequent with combined epidural plus GA compared to GA with postoperative intravenous morphine analgesia for pain management.[62,65]

Hypoxic pulmonary vasoconstriction (HPV) is affected and may be abolished during inhalation anesthesia. Blunting of HPV in the elderly during GA causes a greater incidence of intraoperative V/Q mismatch and an increased alveolar-to-arterial oxygen gradient. Elderly patients have an increased sensitivity to ventilation depression from opioids, benzodiazepines, and inhalation anesthetics because their responses to hypoxia and hypercarbia are impaired. GA has major effects on the pulmonary system because inhalation anesthesia depresses respiratory responses to hypoxia and hypercarbia. Patients experiencing these effects commonly require airway manipulation due to a high propensity of obstruction resulting from respiratory muscle (thoracic) relaxation. These influences can compromise the usual protective responses of the pulmonary system during the perioperative period and must be considered in elderly surgical candidates. Negative effects on pulmonary function from opioids and inhalation anesthetics predispose these older patients to atelectasis, increased risk of hypoxemia and pneumonia, V/Q mismatch, and other postoperative pulmonary challenges.[66]

RA and analgesia with local anesthetics for postoperative pain may provide a greater safety margin for elderly patients compared to systemic or epidural opioids. Using RA and analgesia (without opioids) in the elderly population, especially for patients with severe pulmonary dysfunction, may be more appropriate for postoperative pain relief.[51,67] Oxygen saturation in elderly patients receiving RA and analgesia without an opioid is typically higher, and the use of systemic (and epidural) opioids results in a higher incidence of hypoxic events compared to RA and analgesia with local anesthetics alone.[68] A reduced incidence of pulmonary infection, an increase in PaO_2, and an overall decrease in pulmonary complications are evident with epidural local anesthetics compared to systemic opioids for postoperative analgesia.[42] However, metaanalysis has found that atelectasis is reduced with the use of epidural opioids compared to systemic opioids (for postoperative analgesia) and that epidural local anesthetics (continuous) or local anesthetic-opioid mixtures result in reduced postoperative pulmonary morbidity following major abdominal and thoracic surgery versus systemic opioids.[69,70]

Another metaanalysis has shown that RA (especially epidural analgesia) may decrease pulmonary complications in hip fracture surgery. Patients who received RA had shorter intensive care unit stays and reduced intubation times compared to patients receiving systemic postoperative opioids.[71] A metaanalysis of 141 clinical trials showed a 39% reduction in pneumonia and 60% less pulmonary depression in patients receiving thoracic epidural anesthesia and analgesia versus those who received GA and postoperative patient-controlled analgesia.[17] The reasons why several randomized trials have not demonstrated a consistent statistical advantage of RA in reducing respiratory complications in the elderly may be the lack of differentiation and uniformity of epidural analgesic mixtures; whether or not an opioid or how much opioids (systemic and/or epidural) were used; and the differences in the site of surgery, the timing and duration of RA and analgesia, and the vertebral level of neuraxial blockade insertion.

Endocrine and Immune Systems

Metabolic effects of surgical stress and pain produce hyperglycemia and overall catabolism that may predispose patients, especially critically ill patients, to increased morbidity (polyneuropathy, infection, multiorgan dysfunction/failure) and mortality.[72] RA and postoperative analgesia may maintain the most stable physiological parameters during surgery and theoretically prevent or reduce such surgical stress responses. For example, RA may minimize surgical stress by blocking the activation of the sympathetic and somatic nervous systems. Epidural blockade reduces postoperative hyperglycemia and improves glucose tolerance despite plasma insulin concentrations being unchanged.[59] More stable cardiovascular and hemodynamic responses, as well as attenuation of stress responses to surgery have been demonstrated.[73] The plasma glucose normalization and improved glucose tolerance seen with RA and analgesia can improve perioperative management of optimal glucose control. RA and analgesia can reduce catabolic response to surgery and improve gastrointestinal rehabilitation, economy of proteins, and the nutritional status of surgical patients, especially those undergoing abdominal surgery.[74]

The communicating capability of circulating immune cells and cytokines of the immune system serves as one of the body's major defense systems. Some degree of deterioration of the immune system occurs as human beings age. Reduced cellular and

Table 6. Influence of Aging on the Pulmonary System

Structures	Functional Changes	Results
Conducting Airways (nose to respiratory bronchioles)	1. Change of muscle and cartilaginous support 2. Slow loss of elastin, collagen, and water content, along with muscle atrophy	1. Dry mouth, snoring, bleeding, and mucosal injury possible 2. Predisposition to upper airway obstruction
Diameter of trachea and central airways	1. Increase in size of cartilaginous airways (trachea and bronchi) by 10% 2. Calcification of central airway cartilage 3. Bronchial mucous gland hypertrophy 4. Potential for increased compliance of small and large airways	1. Functional increase in anatomical dead space 2. Compression of airway with forced exhalation 3. Decreased maximum expiratory flow rate 4. Increased residual volume
Upper airway reflexes	1. Depression of protective airway reflexes (sneezing, coughing, etc) 2. Decreased upper laryngoesophageal sphincter contractile reflex 3. Decreased number and activity of respiratory cilia 4. Coughing reflex impairment	1. Increased potential of pulmonary aspiration 2. Increased stimulation necessary to trigger sensory and motor components of airway reflexes
Lung Parenchyma ***Alveolar surface area and elastic recoil***	1. Enlargement of bronchioles and alveolar ducts and shortened alveolar septa 2. Alveolar air decrease with air volume in alveolar ducts increase 3. Reduced surfactant production 4. Lost elastic recoil in lung parenchyma 5. Stiffer chest wall	1. Decreased alveolar surface area (15% by age 70) 2. Airspace enlargement 3. Flattening of the volume-pressure curve of the lung and less lung compliance
Function of lung defenses	1. Decrease in local defenses (cough, mucocilia) 2. Humoral defenses (cellular, immune) reduced by decreased T-cell function and regeneration	1. Failure of T-cell homeostasis
Pulmonary Mechanics ***Chest wall compliance***	1. Calcification of rib cage, vertebral joints and costal cartilage 2. Osteoporosis and vertebral compromise 3. Altered diaphragm affecting force-generating ability	1. Stiffened chest wall and decreased chest wall compliance 2. Increased respiratory work requirements
Respiratory muscles	1. Decreased strength and speed of skeletal muscle contraction 2. Loss of motor neurons 3. Reduced diaphragm strength 4. Shortened rest-length of inspiratory muscles	1. Increased oxygen cost of ventilation (especially with stress and physical activity)
Pulmonary vasculature	1. Reduced volume of pulmonary capillary bed	1. Increased pulmonary arterial pressure and vascular resistance
Lung Volumes and Capacities	1. Increased residual volume due to chest wall stiffness, loss of lung recoil, and decreased muscle strength 2. Decreased FEV1	1. Decreased vital capacity 2. Mild increase of functional residual capacity

Table 6. Continued

Structures	Functional Changes	Results
Expiratory flow	1. Decreased elastic recoil pressure	1. Reduced maximum expiratory flow rate
Gas Exchange ***Diffusing capacity***	1. Loss of functional alveolar surface area	1. Decreased oxygen diffusing capacity 2. Increased arterial-alveolar oxygen gradient
Ventilation/perfusion matching	1. Premature lung airway closure (in tidal volume range) 2. Inspired air distributed at apexes rather than lung bases 3. Airways close at smaller exhaled tidal volume	1. Reduced capillary oxygen tension of basilar lungs 2. Decreased arterial oxygen tension 3. Increased closing volumes 4. Ventilation-perfusion mismatch
Control of Respiration ***Ventilatory responses***	1. Decrement of central and peripheral chemoreceptors	1. Decreased ventilatory response to hypercapnia and hypoxia 2. Increased sensitivity to narcotic-induced respiratory depression 3. Increased disruption of sleep ventilation

FEV1, forced expiratory volume in 1 second.

humeral responses are seen throughout the entire immune system with aging. The thymus gland undergoes an involutionary process, and thymulin secretions decrease as individuals age. Hormones responsible for mature T cell modulation and progenitor phenotypic cell maturation processes are reduced, and the number of T lymphocytes contributed to circulation lessens with age. These physiologic and immunologic processes result in a clinically significant change in function and the overall condition of older individuals in an unstressed state. GA or lumbar epidural anesthesia alone has a minor influence on human immune function in the absence of surgery. Immunological changes with aging become evident when older patients become stressed and move away from homeostatic states. Therefore, measures taken to ensure homeostasis and to reduce the stresses placed on surgical patients will help to preserve the function of the immune system. RA and analgesia can preserve humoral and cellular immune functions in surgical patients (especially for procedures below the umbilicus),[75] whereas GA may worsen the immunosuppression response that can occur subsequent to surgery. Therefore, RA and analgesia (with local anesthetics) may actually decrease postoperative infectious complications from surgery.[75]

ANALGESIC AGENTS

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are the most widely prescribed and used medication in the United States (Table 7).[76] NSAIDs inhibit prostaglandin synthesis, resulting in a drug class that has analgesic, antipyretic, and antiinflammatory activity. Even more specific, selective cyclooxygenase-2 (COX2) inhibitors have the additional benefits of reducing the incidence of GI side effects and positively influencing cardiothromboembolic events.[77]

A study conducted by McDaid et al demonstrated that NSAIDs reduced morphine requirements in patient-controlled analgesia following major surgery, and patients had a concomitant reduction in morphine-related AEs of sedation, nausea, and vomiting.[78] Another investigation reported that ibuprofen and celecoxib reduced pain and opioid pain medication needs after ambulatory surgery, enhancing patients' satisfaction and the quality of their recoveries.[79] NSAID administration (when not contraindicated relatively or absolutely) has become one of the go-to nonopioid drug alternatives included in practice guidelines for acute pain management in the perioperative setting.[25]

Intravenous Acetaminophen

A non-NSAID analgesic, intravenous acetaminophen has recently become available with platelet-sparing properties (Ofirmev, Cadence Pharmaceuticals, San Diego, CA) and has been incorporated into multimodal analgesic perioperative protocols in several surgical institutions.[80]

Antidepressants

Certain antidepressant drugs are widely used to treat neuropathic pain (characterized by damage to or

Table 7. Nonsteroidal Antiinflammatory Drugs

Salicylates	Aspirin
	Diflunisal
	Salsalate
Fenamates	Diclofenac
	Ketorolac
	Meclofenamate
	Mefenamic acid
	Tolmetin
Acetic acid derivatives	Etodolac
	Indomethacin
	Sulindac
Propionic acid derivatives	Fenoprofen
	Flurbiprofen
	Ibuprofen
	Ketoprofen
	Naproxen
	Oxaprozin
Enolic acid derivatives	Meloxicam
	Nabumetone
	Piroxicam
COX2 selective inhibitor	Celecoxib

dysfunction of the CNS and/or PNS). However, they have also become popular as a nonopioid component multimodal treatment of postoperative pain (Table 8). Antidepressants have several mechanisms of action that include calcium channel blockade, inhibited reuptake of the chemical mediators of serotonin and norepinephrine, sodium channel blockade, activation of opioid receptors, and action as an N-methyl-D-aspartate receptor antagonist.[81] These medications are classified according to their mode of action and include monoamine oxidase inhibitors type A, traditional tricyclic antidepressants, selective norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors.

Table 8. Antidepressants

Tricyclic antidepressants	Amitriptyline
	Clomipramine
	Desipramine
	Imipramine
	Maprotiline
	Nortriptyline
Monoamine oxidase inhibitors	Selegiline
	Tranylcypromine
Selective serotonin reuptake inhibitors	Citalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
Selective norepinephrine reuptake inhibitors	Desvenlafaxine
	Duloxetine
	Venlafaxine

Multimodal incorporation of an antidepressant medication into perioperative pain management also has advantages, in addition to the drug's value as an analgesic, of improving a patient's sense of well being, reducing fatigue, and being nondisruptive of the sleep pattern. A patient's failure to respond to treatment with antidepressants could be attributable to low drug plasma concentrations secondary to poor patient compliance or inadequate drug absorption. Therefore, monitoring medication concentration, drug-to-drug interactions, and adverse drug reactions may be useful in situations of treatment failure.

Anticonvulsants

Anticonvulsants are also commonly used to treat neuropathic pain as a component in a multimodal treatment protocol (Table 9). The basis of this drug group's effectiveness on pain relief appears to be related to aspects of the pathophysiology of epilepsy (both conditions being characterized by neuronal

Table 9. Anticonvulsants

Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Valproic acid
Topiramate
Baclofen
Pregabalin
Gabapentin

hyperexcitability). The hyperexcitable state of neuropathic pain conditions and epilepsy is marked by sensitization (reduced thresholds) along with dysfunctional discharges at the dorsal root ganglion or the spinal dorsal horn.[82]

Anticonvulsants are FDA approved for a host of neuropathic pain syndromes. Examples include carbamazepine for trigeminal neuralgia and gabapentin for postherpetic neuralgia. Mechanisms of action include inhibition of gamma-aminobutyric acid and modulation of voltage-gated sodium and calcium channels. Multiple studies have demonstrated the efficacy of anticonvulsant medication therapy as an adjunct in multimodal pain management.[83] Anticonvulsants such as gabapentin and pregabalin have a route of renal excretion (an advantage for older patients with liver compromise), few drug-to-drug interactions, the benefit of rapid titration with early onset of analgesia, and linear pharmacokinetics. However, this class of adjuvant has dose-dependent side effects including dry mouth, somnolence, dependant edema, and dizziness.

Muscle Relaxants

Medications with multiple modes of action are cyclobenzaprine and tizanidine—the skeletal muscle relaxants that have been used as adjuncts in multimodal pain therapy. The comparative efficacy of these drugs is not well known in the elderly. Evidence from clinical trials is limited, and a distinction that needs to be understood is that skeletal muscle relaxants consist of antispasticity and antispasmodic agents. Antispasticity medications—baclofen, diazepam, tizanidine, and dantrolene—aid in improving muscle hypertonicity and involuntary jerking movements, while the antispasmodic agent, cyclobenzaprine, is used to treat musculoskeletal conditions (such as fibromyalgia) in the elderly. Therefore, the choice of skeletal muscle relaxant for multimodal pain therapy should be based on indication, patient tolerability, and AE profile.

An early animal study by Commissiong and colleagues [84] identified the analgesic properties of cyclobenzaprine and suggested that it activates the locus ceruleus in the brainstem, increases the release of norepinephrine in the ventral horn of the spinal cord, and inhibits alpha motor neurons. Caution must be used when prescribing cyclobenzaprine to elderly patients with arrhythmias and congestive heart failure and to patients in acute recovery following a myocardial infarction.

An alpha 2-receptor agonist and centrally acting skeletal muscle relaxant, tizanidine, inhibits the release of excitatory amino acids from spinal neurons. It is chemically related to clonidine but has less antihypertensive effect; however, use with caution is recommended in patients with impaired renal function. Tizandine has been shown to be helpful in elderly patients with spasticity caused by spinal cord injury and traumatic brain injury, as well as in patients with multiple sclerosis and low back and neck pain.

Steroids

Steroid medications (corticosteroids) useful for pain management include those with large antiinflammatory activity and those with low water balance. Glucocorticoids act by suppressing the inflammatory response, and mineralocorticoids act by modifying both salt and water balance. These steroid preparations are used as injectables for intraarticular, epidural, periarticular, and intramuscular administration (Table 10). Studies evaluating postoperative pain scores, lengths of hospital stay, and morphine use in patients who had lumbar spine surgery have shown evidence of improved efficacy in those receiving a steroid preparation.[85] However, continued controversy exists over the extent to which corticosteroids influence wound healing.

Topical Analgesics

Topically applied single or multiagent analgesics are used as an adjunct in pain management scenarios. Topical agents include lidocaine, capsaicin, and diclofenac. A lidocaine patch (Lidoderm) can reduce ectopic activity in the voltage-gated sodium channels of damaged sensory nerves and also acts as a mechanical barrier to relieve allodynia. Capsaicin stimulates transient receptor potential vanilloid receptors and subsequently depletes substance P from sensory nerve fibers. Additional uses include treat-

Table 10. Corticosteroids

Methylprednisolone acetate
Triamcinolone acetonide
Triamcinolone diacetate
Betamethasone
Dexamethasone

ment for low back pain and for painful diabetic peripheral polyneuropathy.

GENERAL ANESTHESIA

The role of GA in brain toxicity and its influence on perioperative pain management and POCD have been discussed as a potential pathogenic factor in the elderly.[86,87] These findings imply that the consensus that modern anesthetics are completely reversible may not be entirely correct. In addition, these findings also imply that a difference in perioperative outcome would be evident after local anesthetic techniques versus GA, but no correlation between anesthetic technique and AEs, long-term pain management advantages, or reduced incidence of POCD has been found. However, short-term gains diagnosed at approximately 1 week after surgery have been achieved with local anesthetic procedures compared to GA.[20]

CONCLUSION

Despite advanced pain management modalities and drug delivery systems, perioperative pain management in the elderly continues to be an issue of concern. Patients and healthcare providers have become increasingly aware of inadequate postoperative pain relief and the need to better implement current postoperative pain management treatment paradigms and to develop new pain management methods for all patients.

Fortunately, the increasing use of multimodal analgesia has resulted in improved pain control for postoperative elderly patients. By incorporating a combination of medication therapies (considered to have subclinical or incomplete effects if used alone) and preemptive analgesia, such treatment can be used to effectively treat postoperative pain.

Elderly patients often present with age-related changes of the nervous system, and whether these changes are normal or pathologic, they must be considered in the perioperative anesthetic plan and during the selection of appropriate postoperative pain management. The older patient's perioperative evaluation for any surgical procedure should be performed by a multidisciplinary team focused on optimal postoperative pain management, recovery, therapy, and long-term follow-up when indicated. A routine anesthesia assessment plan should be established that is based on the effects of aging and the decreases of functional reserve in both the CNS and PNS. With this level of preparation, multimodal analgesia along with RA may ensure the elderly patient's rehabilitation and transfer to an outpatient setting more expeditiously after major surgery and improve recovery while reducing the use of healthcare resources and costs.

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