Postoperative Analgesia in Geriatric Patients

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ABSTRACT

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Effective postoperative analgesia in geriatric patients is both challenging and rewarding. Inadequate pain control after surgery is associated with adverse outcomes in the older patient. This review will attempt to describe the difficulty with assessment of pain and variations in pain experience of elderly patients. Physiological changes related to aging need to be also carefully considered, because aging is individualized and progressive. Pharmacokinetic and pharmacodynamic changes in geriatric patients, the higher incidence of co-morbidities and concurrent use of other drugs, must be carefully adjusted to suit each geriatric patient, concerning postoperative pain management. Medication for postoperative pain will be discussed. Unfortunately, many medications have not been studied well in the older population. Non-pharmacological approaches to postoperative pain management will not be discussed, although this would be an interesting topic for further discussion.

INTRODUCTION

Advanced diagnostic and therapeutic facilities have enhanced the life expectancy of humans, as a result of which geriatric population is expected to increase 25% by 2020 worldwide[1]. In Greece, according to the last population census conducted at 2011, in a total of 10.787.690 population, the residents above the age of 65 were 1.873.245[2]. Life expectancy in Greece increased from 77,79 years in 1996 to 79,05 in 2004 and 80,2 years in 2009[2] .Given that the elderly undergo surgery four times more often than other age groups, anesthesiologists can look to the future and see a time when the majority of surgical patients will be older than 65 years and many older than 80 years[3]. In 2007, approximately 35% of surgical procedures, in USA, were performed in patients 65 years and older[4]. Although the criteri-

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on of 65 years of age and greater is followed worldwide for classifying this subset of population into geriatric category, the biological age, which results from cellular aging, is more important than the chronological age in defining the capacity of the elderly to cope with the massive surgical and anesthetic stress[5,6,7]. Age is considered as one of the strongest predictors in population undergoing anesthetic stress. As a result, mortality increases twofold in this subset of population as compared to young healthy adults, especially in patients undergoing major surgery[5,8]. Therefore, it is necessary that the national health system adjusts to the new data and also insures the quality of the services, including postoperative pain management services, provided to this group of patients.

Elderly surgical patients often have multiple co-morbid conditions that limit their functional capacity and recovery and increase the risk of severe complications. They also take more prescription medications; on average two to five medications per person[9]. Additionally, inappropriate prescribing of medications places the older patient at risk for adverse reactions and preventable hospitalizations[10]. Unfortunately, nearly 35% of medication trials exclude older patients based on age alone[11].Therefore, the effect of aging on pharmacokinetics and pharmacodynamics of drugs is incompletely characterized. Preoperative assessment in geriatric patients is very important for the detection of all the co-existing diseases in these patients. Co-morbid pain conditions, in elderly patients, such as osteoarthritis have been associated with decreased functional status at one and three months post hospital discharge[12]. Preventive actions such as positioning during and after surgery can reduce pain from these sources[12].

The purpose of this article is to discuss major clinical issues specific to the management of postoperative pain in geriatric patients.

INADEQUATE POSTOPERATIVE PAIN RELIEF AND CONSEQUENCES IN ELDERLY PATIENTS

Inadequately postoperative pain management in elderly patients has a great impact on physical, psychological and cognitive symptoms, and consequently, on the overall quality of life. The endocrine system reacts to pain by releasing an excessive amount of hormones, ultimately resulting in carbohydrate, protein, and fat catabolism (destruction); poor glucose use; and other harmful effects[13]. This reaction combined with inflammatory processes can produce weight loss, tachycardia, increased respiratory rate, fever, shock and death. Continuous, unrelieved pain activates the pituitary-adrenal axis, which can suppress the immune system and result in postsurgical infection and poor wound healing[13].

Sympathetic activation can have negative effects on the cardiovascular, gastrointestinal, and renal systems, predisposing patients to adverse events such as cardiac ischemia and ileus. The cardiovascular system responds to stress caused by pain by activating the sympathetic nervous system, which produces a variety of unwanted effects. In the postoperative period, these include hypercoagulation and increased heart rate, blood pressure, cardiac work load, and oxygen demand. Aggressive pain control is required to reduce these effects and prevent thromboembolic complications. Cardiac morbidity is the primary cause of death after anesthesia and surgery[14].

Postoperative pain is the most important factor responsible for regional impairment of ventilation, ineffective cough reflexes and gecrease ability to sigh and beath deeply, resulting in atelectasis, hypoxemia, infection and respiratory failure[14].

All above mentioned postsurgical complications, related to inadequate pain management, negatively affect the patient's welfare and the hospital performance because of extended lengths of stay and readmissions, both of which increase the cost of care.

Continuous, unrelieved pain also affects the psychological state of the patient and family members. Common psychological responses to pain include anxiety and depression. Between 8% and 20% of older patients display depressive symptoms and depression has been associated with worsened pain[15]. Additionally, postoperative pain in geriatric patient has been associated with increased sleep disturbances, decreased socialization and impaired ambulation[16]. Reasons for inadequate pain control include lack of training, inappropriate pain assessment, and reluctance to prescribe opioids[10].

Postoperative cognitive dysfunction can be usefully defined as a long term, possibly permanent, disabling deterioration in cognitive function following surgery[17]. The risk of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) increases with age[18]**.** Although the overall prevalence of postoperative delirium in elderly adults after major elective surgery has been estimated to be 10%[17], for special procedures such as hip fracture repair, the rate of incident postoperative delirium has been reported to be as high as 40%[19]. POD and POCD are also associated with preoperative cognitive impairment, vision impairment, depression and other common comorbidities, such as vascular disease and renal dysfunction[11]. POCD may be independent of the type of anesthesia received[11,18]. Although it may be assumed that general anesthesia and complex surgery would result in an increased likelihood of POCD, a recent study challenges this assumption[20]. In this study, patients who received procedural sedation had the same risk

of cognitive decline, as those undergoing elective total hip joint replacement surgery or coronary artery bypass surgery. Cognitive impairment may make pain assessment more difficult, and many practitioners express concern regarding evidence that opioid administration may precipitate postoperative delirium[17].

Poorly managing of pain may put also clinicians at risk for legal action. Having standards of care in place increases the risk of legal action against clinicians and institutions for poor pain management and there are instances of law suits, in USA, filed for poor pain management by physicians[21].

ASSESSING AND EXPERIENCING PAIN IN GERIATRIC POPULATION

The majority of older adults describe moderate to severe pain at some point after major surgery[22]. Even though older adults report pain similar to middle-aged and younger adults[23]and have similar opioid needs in the post-anesthesia care unit[22] older adults continue to be undertreated for postoperative pain.

Assessment of pain in the older adult can be complicated by numerous factors, including difficulties with communication, the high prevalence of disability, dementia and sensory disturbances in this population[11]. Postoperative pain assessment during movement provides a more accurate pain measure than assessment at rest[23].

Cognitively impaired patients are known to be at greater risk of undertreatment of acute pain[24]. Patients with hip fracture, with POCD received one third the amount of opioid analgesia as compared to cognitively intact patients. The majority of dementia patients were in severe pain postoperatively[25].

Assessment of pain in the older adult can be more time consuming and difficult and an assessment should include, if possible, direct patient response, provider observation, as well as input from family and/or caregivers. Various tools for assessing pain have been developed and several have been validated in the older population such as Verbal Rating Scale (VRS), Visual Analogue Scale (VAS), Numerical Rating Scale (NRS) and Faces Pain Scale[11]. Elderly patients have been reported to experience more difficulties with VAS[14]. Jensen et al., observed that there was a significant correlation between age and incorrect response to VAS scores[26]. Even if the VAS is the most frequent used method, the NRS and the VRS seem to be the preferred scales[14]. Gagliese et al., observed that age differences in pain scores depended on the scale used[23]. Table 1 summarizes several pain assessment tools that have been validated in the elderly[11,27]. In patients with POCD or POD assessment of pain is more challenging. The Check-list of Nonverbal Pain Indicators

(CNPI), a behavioral observation scale for nonverbal older adults with severe cognitive impairment is one of the more rigorously tested pain assessment instruments[22].

Several studies have suggested that elderly patients report lower pain intensity than younger patients[14]. This is thought to be due to the misconceptions that pain is a normal part of aging, pain perception decreases with age, older people who do not complain of pain are not in pain, and pain reports may be a way of seeking attention[11]. Also, pain-transmitting C and Aδ peripheral nerve fiber function declines progressively with age[11]. Postoperative pain has been reported to be less in older persons and diminish with time[28]. The point, at which pain is first felt experimentally, is likely slightly higher. However, pain tolerance, the maximum pain level endured, is probably reduced[14].

Preoperative pain management education for older adults can significantly reduce their postoperative pain[29]. Pain management content should provide a general overview of pain that includes defining pain, understanding the causes of surgical pain, how to use pain assessment scales, and the importance of both preventing pain and managing pain that does occur pharmacologically.

Table 1. Pain assessment tools.

Tool	Description	Discussion
Visual Analogue Scale	A vertical or horizontal 100-mm line anchored by verbal descriptors such as 'no pain' and 'worst pain possible'. Patients make a mark on the line that represents their pain intensity	Requires abstract thought Difficult to use in cognitively or visually impaired May be less valid in older adults
Numerical Rating Scale	Available in a variety of scale ranges and anchors, such as 0–10, with 0 being 'no pain' and 10 being 'worst pain possible'	Requires abstract thought Valid in cognitively impaired Commonly recommended scale for pain assessment in older adults
Verbal Descriptor Scale	Available in a variety of scale types (e.g., pain thermometer, present pain intensity index and graphic rating scale)	Limited amount of choices Requires some command of language Highly preferred by older adults Low failure rate in cognitively impaired
Faces Pain Scale	Consists of seven faces ranging from neutral face (no pain) to grimacing face (worst pain possible)	Requires abstract thought Difficult to use in cognitively impaired May be less preferred by older adults
Behavioral Pain Scale	Observational assessment tool for nonverbal patients compiled by nurse or physician	Generally takes longer to complete Requires knowledge of how scale is used Better results if observer is very familiar with patient

PHYSIOLOGICAL CHANGES OF AGING

Aging is characterised by a failure to maintain homeostasis under conditions of physiological stress. Physiologic changes associated with decrease in viability and an increase in vulnerability. This means that older people present progressive decrease in organ function and progressive loss of organism reserves, but the idiosyncratic factor loss of reserves is important. The co-existence of morbid situations in the elderly affects the regulating mechanisms and restricts the responsiveness in stress conditions, such as postoperative pain.

Aging is typified by changes in the cardiovascular system. The biggest change in the cardiovascular system is the decrease in cardiac output (CO) and vascular resistance.The decrease in CO is about 1% every year after the age of 30[14]. Aging heart is volume dependant and volume tolerant. Small changes in intravascular volume or venous capacitance may induce cardiovascular instability. Also, there is a decrease in autonomic nervous system responsiveness, such that following spinal or epidural anesthesia, there is an increased risk of profound hypotension. In addition, the decrease in CO induces a decrease in hepatic blood flow. Clearances of opioids would be unafected by the activity of hepatic enzymes but sensitive to hepatic blood flow. Thus a 25% to 40% reduction in clearance could be expected secondary to reduce hepatic blood flow in geriatric patients[14]. The initial high arterial concentration observed in the first few minutes after injection of an i.v bolus dose is a function of this dilution with CO and the kinetics of the first pass of the drug (e.g morphine) through the lungs. Thus, a 0% to 20% reduction in CO would lead to higher peak arterial concentrations after i.v administration. Therefore, the initial dose should be reduced and also slow injection rate should be used in elderly patients[30]. Degenerating alterations are causing a decrease in contractility and sensitivity of adrenergic receptors, reduction of co-pliance of the heart muscle and increase the incidence of arrhythmias[14]. Also, in these patients co-exists usually arterial hypertension, diastolic dysfunction and valvular heart disease. The changes of vessels that progressively lose their elasticity and small changes of intravascular volume may lead to hemodynamic disorders, after regional analgesia or high dose of opioids. Inadequate treatment of postoperative pain leads to an increase of arterial blood pressure and heart rate and that can lead to an increase of oxygen consumption, which may cause ischemic heart failure and infraction[31].

The impairment of respiratory function is caused by structural changes in the lung tissue and chest wall. There is a decrease in sensitivity of the respiratory centres to hypoxia and hyper-

capnia. Furthermore, elderly patients have increased periodic breathing or apnea periods during sleep, which makes them more likely to have apnea and airway obstruction in postoperative period. There is an increase risk of hypoxemia, in elderly patients that require opioids[14].

Aging is associated with a decrease of neuronal and neurotransmitter density and activity. Also, there is a decrease of the number of neurotransmitter receptor sites[14]. Additionally, age reduces β-endorphins levels, the synthesis of γ--aminobutiric acid (GABA) and serotonergic receptors[32]. Brain atrophy characterises the elderly patients and is caused due to a decrease in neuron size. The decrease of the number of neurons of the autonomic nervous system can also cause hemodynamic disorders[11].

Renal function declines progressively with age. There is a decrease in the glomerular filtration rate (GFR 1% to 1,5% per year after 2nd decade), secondary to decreased renal blood flow (10% per decade in the adult years). The combination of reduced kidney mass and reduced glomerular function leads elderly patient to be more prone to dehydration, sodium loss and impaired fluid handling. Co-existing diseases such as diabetes, arterial hypertension and vascular disease play a significant role in worsening renal function in elderly patients[14]. Decreased glomerular filtration rate may be balanced by an age-related decrease in muscle mass, and therefore, creatinine may not be a reliable indicator of glomerular filtration rate in the elderly[11].On average, glomerular filtration rate decreases less than 1 ml/min/year after middle age[33].The aging kidney is more sensitive to pain and surgical stress due to the decreased renal blood flow and decreased response to vasoconstriction. Decreased renal function can lead to toxic accumulation of drugs and metabolites, if dosing is not adjusted according to renal clearance

Advancing age is associated with a progressive reduction in liver volume and liver blood flow[14]. Alteration of hepatic structure and enzymatic functions with ageing is moderate. In healthy elderly person, routine tests of liver function involving the metabolism and elimination of specific dyes, radioisotopes, and protein synthesis do not show significant differences between individuals aged 50–69 and 70–89 years[33].

The main changes involve the secretion of hydrochloric acid and pepsin, which are decreesed under basal conditions. This may be the direct consequence of changes in the enzyme secreting cells and organs or hormonal and neural regulatory alterations[33]. By contrast, gastric emptying in elderly subjects is similar to that of young subjects[33]. Disorders of gastric mucosa make elderly patients more sensitive to mucosa injuries from the use of NSAIDs[14].

PHARMACODYNAMIC AND PHARMACOKINETIC CHANGES IN THE ELDERLY PATIENTS

With age, the pharmacodynamics and pharmacokinetics of drugs change. Pharmacodynamics is usually related to specific drug receptors, which can change in function and density with age.The number and the affinity of receptors for neurotransmitters present in a tissue decreases with age[11]. Older adults display pharmacodynamic changes, particularly in the central nervous and cardiac systems. Advancing age is also associated with increased sensitivity to the central nervous system effects of benzodiazepines and opioids[14]. Sedation is induced by diazepam at lower doses and lower plasma concentrations in elderly subjects[33]. The sedating effects of benzodiazepines can be increased by up to 50% despite the pharmacokinetics being similar between the young and old[11]. Autonomic nervous system dysfunction, impaired thermoregulation and reduced cognitive function may affect drug responses, in elderly patients[14]. The loss of homeostasis in geriatric population can lead to hemodynamic disorders or delirium, after the use of local anesthetic drugs for regional anaesthesia[14]. Pharmacodynamic interaction may occur with synergistic effects when taking more than one sedative or anticholinergic agent resulting in delirium, sedation, urine retention or constipation[14]. Table 2 summarizes the selected pharmacodynamic changes with ageing.

Table 2. Selected pharmacodynamic changes with ageing.

Drug	Pharmacodynamic effect	Age-related change
Adenosine	Heart-rate response	↔
Diazepam	Sedation, postural sway	↑
Diltiazem	Acute and chronic antihypertensive effect	↑
	Acute PR interval prolongation	↓
Diphenhydramine	Postural sway	↔
Enalapril	ACE inhibition	↔
Furosemide	Peak diuretic response	↓
Heparin	Anticoagulant effect	↔
Isoproterenol	Chronotropic effect	↓
Morphine	Analgesic effect	↑
	Respiratory depression	↔
Phenylephrine	α_1-adrenergic responsiveness	↔
Propranolol	Antagonism of chronotropic effects of isoproterenol	↓
Scopolamine	Cognitive function	↓
Temazepam	Postural sway	↑
Verapamil	Acute antihypertensive effect	↑
Warfarin	Anticoagulant effect	↑

↑ = increase; ↓ = decrease; ↔ = no significant change; ACE = angiotensin-converting enzyme.

Pharmacokinetic studies on the effect of ageing on drug absorption have provided conflicting results. Some studies have not shown significant age-related differences in absorption

rates for different drugs[34]. The absorption of vitamin B_{12}, iron and calcium through active transport mechanisms is reduced[35] whereas the absorption of levodopa is increased, probably secondary to a reduced amount of dopadecarboxylase in the gastric mucosa[33].

Hepatic metabolism of drugs relies on two important steps, Phase I and Phase II metabolism. The oxidation, reduction and hydrolysis reactions of Phase I metabolic capability probably decrease with age, but this may or may not be clinically significant[11]. The Phase II reactions of conjugation through methylation, sulfation, acetylation or glucuronidation are likely unaltered with aging[11]. As mentioned before, decreased hepatic blood flow and mass can lead to reduced metabolism and prolonged elimination, especially for drugs with blood flow limited metabolism, such as morphine.

The consequence of renal impairment on the pharmacokinetics of analgesic drugs typically outweighs the potential impact of reduced hepatic function[36]. For example, renal insufficiency can play a significant role in the reduced clearance and accumulation of both drugs and drug metabolites. Morphine and its metabolites (morphine-6-glucuronide and morphine-3-glucuronide) and meperidine and its metabolite (normeperidine) are probably the most clinically relevant[11].

Changes in the percentage of body water and fat, with reduction of water and increase of body fat, causes an increase in the concentration of the drug in the blood. Fat-soluble drugs such as diazepam and fentanyl have an increased volume of distribution, whereas drugs that are water-soluble have a decreased volume of distribution[14].

Geriatric patients present decreased production and concetration of albumin (which binds acidic drugs), that can cause an increase of the free fraction of the drug in the plasma and a reduction in the degree of plasma protein binding drugs[14.] Protein binding of lidocaine in elderly is increased as is the elimination half-time and there is a reduction in clearance of local anesthetic drugs. The dose of local anesthetic required to achieve a given sensory level during epidural anesthesia is often perceived to be less with aging, although some reports describe a linear relationship between dose and age[14].

Because of the wide variation of physiological parameters present between geriatric patients, the expression «start low and go slow» should be always remembered when initiating drug therapy in the older patient[11].

POSTOPERATIVE ANALGESIC TECHNIQUES AND AGENTS FOR GERIATRIC PATIENTS

A multimodal approach to analgesia is critical to help older adults achieve maximum pain re-

lief and avoid side effects from analgesics. Addition of non-opioid analgesics to the regimen can increase pain relief and reduce the opioid dose. Advances in the knowledge of molecular mechanisms have led to the development of new pharmaceutical products to treat postoperative pain in elderly patient.

Regional techniques

Over the past 20 years, anesthesiologists have played a more aggressive role in the treatment of postoperative pain. In addition to designing anesthetic techniques, to minimize the impact of pain through the use of tailored pharmacologic interventions, many anesthesiologists include the extended use of anesthetic techniques, such as epidural, intrathecal analgesia and nerve blocks.

Epidural postoperative analgesia

Epidural postoperative analgesia can provide great pain relief[37] and is frequently used with older adults patients[22] for postoperative pain management.

Epidural analgesia is an excellent option for pain control following upper abdominal and intrathoracic surgical procedures[14]. In elderly patients, epidural opioid and local anesthetic combinations are very effective analgesics, consistently demonstrating lower pain scores with significantly lower systemic opioid exposure, compared to intravenous opioid administration[15]. Analgesia via epidural route after elective colon surgery, using bupivacaine and morphine, accelerates postoperative recovery of gastrointestinal function, provides quicker mobilization and reduces hospital stay[38].

Continuous epidural analgesia (PCEA) improves early rehabilitation, after knee surgery, compared with the patient-controlled analgesia group (PCA)[14]. Another study compared the efficacy and safety of PCEA and PCA, after major abdominal surgery, in elderly patients[37]. Pain relief was better at rest and at movement in the PCEA group during the first 5 postoperative days[37]. Cardiorespiratory complications and the incidence of delirium were similar between the 2 groups[37].

Despite that PCEA reduced significantly systemic opioid consumption compared to PCA, epidural analgesia does not appear to offer a significant advantage over intravenous opioids with respect to central nervous system side effects, including respiratory depression, sedateon, and pruritis[39].Local anesthetics are helpful in reducing the amount of opioid needed, but may introduce a greater risk of hypotension, pressure sores, and peripheral nerve compression injuries[15]. A reduced epidural dose of local anesthetic and opioid and frequent monitoring decreases the possibility of toxic effects[37].

A major advantage of epidural analgesia is that it can provide continuous pain control without disruption. Although there are occasional te-

chnical and anatomic difficulties due to advanced age, when epidural analgesia works well, it can provide a near pain free experience.

Intrathecally opiod administration

Intrathecal morphine provides effective analgesia after hip or knee arthroplasty, after gynaecologic surgery or prostate transurethral resection[14]. Intrathecal morphine may be associated with dose-related side effects like nausea, vomiting, drowsiness, urinary retention or delayed respiratory depression. According to Murphy et al., 100μg intrathecal morphine seems to provide the best balance between analgesic efficacy and adverse effects, in elderly patient after hip surgery[40].

Peripheral nerve blocks

Peripheral nerve blocks provide excellent postoperative analgesia without significant complications. Many extremity surgeries are conducted with brachial and femoral plexus nerve blocks and those prove to be useful options in reducing pain in the early postoperative period[15]. While they seldom provide more than 8-10h of anesthesia, they do allow for significant reductions in consumption of opioids during the first postoperative day.

Peripheral nerve blocks effects may be extended through the use of a continuous analgesic infusion via a catheter introduced into the appropriate neural plexus. Catheter placement increases even more the duration of analgesia and upgrades the mobilization and comfort of the geriatric patients[41]. Probably that occurs because of the reduced excretion of the local anesthetic and the slowest action on the peripheral nerves[41]. Since most of these patients are able to transition to oral medications following the majority of extremity surgeries, this is a useful approach for ambulatory procedures, as the nerve block may allow for fewer opioid side effects as well as a reasonably comfortable first night. In-dwelling plexus catheters may be inserted at the time of the initial nerve block, which will allow a continuous infusion or repeated bolus injections of local anesthetic; however, these techniques have not yet gained wide-spread acceptance outside of few academic centers. For selected patients, this may be an option if the patient is anticipated to encounter severe pain, poorly tolerates systemic analgesics, or if dense analgesia is required for repeated manipulation[15].

Continuous local anesthetic infusion through catheter

Pain control infusion pumps automatically and continuously deliver local anesthetic through an intraoperatively placed catheter. Continuous local anesthetic models have been examined in the shoulder and knee[42]. Evidence supports the use of pain control infusion pumps in cardiovascular, cardiothoracic, obstetric, and orthopedic surgery[42]. Unfortunately, the chondrotoxity associated with local anesthetic delivery, in orthopedic knee surgery, has made intrarti-

cular application a dangerous and unpopular choice for postoperative pain control[42].

In this analgesic technique, there are specific problems concerning the local anesthetic catheter placement. As some of the catheters are invariably accidentally prematurely partially pulled out, patients may not receive the benefits of pain control infusion pumps. Intuitively, when placed on suction, effective drainage may work against pain control infusion pump infusion. It is also unclear how much of the local anesthetic remains in the surgical site. High concentrations of local anesthetic have been found in the copious drainage at the site of the catheter–skin in-terface[42]. Lastly, the ideal concentration of local anesthetic catheter has not been identified. The cardiotoxic effects of local anesthetic are real and dangerous, especially for elderly patients. For these reasons in bilateral total knee arthroplasty, patients receive twice the volume but half the local anesthetic concentration in each operative knee in comparison to patients undergoing unilateral procedures[42]. This lower concentration may be inadequate to control pain.

Systemic analgesic agents

Opiods

Opioids remain the gold standard for the treatment of moderate to severe acute pain. The choice of opioid for most of older adults remains morphine sulfate[22]. In literature the use of oxycodone and hydromorphone for postoperative analgesia, in elderly, is widely spread[22]. Certain opioids should be avoided in elderly patients when possible. Propoxyphene is thought to be no more effective than aspirin or acetaminophen, but it is associated with ataxia, dizziness, and neuroexcitatory effects due to drug accumulation[22]. Meperidine hydrochloride should not be used because of the accumulation of a nephrotoxic metabolite[22].

Morphine is a potent opiate analgesic that can be administered orally, intramuscularly, subcutaneously and intravenously. Postoperative i.v morphine titration is used to obtain rapid and complete postoperative pain relief[30]. Because of rapid onset of analgesia, small i.v bolus doses permit titration of the dose of morphine needed to provide adequate analgesia[14]. Aubrun F. et al.[30] proved that i.v morphine titration can be safely administrated to elderly patients using the same protocol, as that used in younger patients. According to the study protocol, when VAS scores in the PACU increased more than 30mm, i.v morphine was titrated every 5 minutes by 2-or 3-mg bolus do-es, until pain was relieved (pain defined by a VAS score less than 30mm). Nevertheless, these results apply only to short-term control of pain in the PACU and not to long-term use of morphine. However, these results may not apply to a frail geriatric population or to patients with severe POCD[14].

The mean elimination half-time for morphine is 4,5 hours in elderly, significantly longer than 2,9 hours that has been observed in younger patients. There is a decrease volume in distribution, a 50% reduction in clearance and a reduction of protein binding[30]. Intravenous morphine can be safely used in cognitively intact older patients[11]and additionally, to the lasting analgesic effect, morphine is inexpensive.

Morphine is broken down in the liver to pharmacologically active metabolites (morphine-6-glucuronide and morphine-3-glucuronide), which are then excreted by the kidneys. In the setting of renal impairment, these metabolites can accumulate, causing respiratory depression and/or neuroexcitation. In the setting of renal impairment, opioids that do not have active metabolites, such as fentanyl, are preferred for continuous use (PCA).

Oral oxycodone is also being administered with increased frequency as part of a multimodal approach to acute postoperative pain[11,43]. Oral oxycodone undergoes less first-pass metabolism and has higher bioavailability than oral morphine[43]. This results in more consistent plasma levels post-administration. Unlike morphine, renal impairment does not appear to affect plasma concentrations of oxycodone or it's active metabolite oxymorphone[11].The administration of scheduled controlled-release oxycodone may avoid the peaks and troughs associated with i.v bolus dosing, resulting in stable plasma levels and improved pain control. Scheduled oral oxycodone (controlled release) improved patients' pain control, patient satisfaction, and decreased postoperative nausea and vomiting compared with i.v morphine PCA in patients after post-lumbar discectomy[44].

Increased sensitivity to opioids appears to be the result of both pharmacokinetic and pharmacodynamic changes[14]. Older persons likely express a lower density of μ-opioid receptors making them more vulnerable to the effects of opioids[22]. Although, older adults experience more frequently side effects from opioids. Aubrun F. et al.[30] showed that acutely, after surgery, in PACU, the total dose of morphine, pain relief achieved and risk of adverse events was not significantly different in older than in younger patients[30]. Side effects, such as nausea, vomiting, sedation, itching, constipation, and respiratory depression, tend to define the limits of clinical therapy. Pain in most patients can be controlled without encountering excessive side effects, but side effects may limit satisfactory pain relief. In these patients aggressive management of the side effects becomes an essential component of providing adequate pain control[30].To adjust for the potential age differences and to reduce the incidence of side effects, the opioid dose should be started at a dose 25-50% lower than the recommended dose for adults and increased slowly by 25-50% in-

crements until the person reports satisfactory pain relief or a 50% reduction in pain intensity is achieved[22]. Opioids should be withheld, if the patient is sedated when awake and/or has a respiratory rate of less than 8 breaths per min[22]. Prophylaxis to prevent constipation should be initiated postoperatively and bowel function monitored. If nausea and vomiting occur, metoclopramide use avoids the anticholinergic side effects of many antiemetics[22].

Opioids, often, are underutilized, or even withheld, in the elderly postoperative patient, especially among individuals experiencing cognitive impairment. The more severe the communication deficit, the more likely the patient will have opioids limited, out of concern that they are contributing, or will contribute to the development of postoperative delirium[18]. Although sedative medications may contribute to delirium, several studies suggest that the opioid use for postoperative pain displays an inverse relationship[15]. Elder patients, undergoing surgical repair of a hip fracture, who received less than 10mg of morphine per 24h span, were more likely to develop postoperative delirium[15].

An extensive literature has documented that long-acting benzodiazepines, tricyclic antidepressants, serotonin selective antidepressants, and anticonvulsants contribute to the likely-hood of falling in the over 65 year old population. Although the opioids are sedatives, the existing literature does not strongly implicate the opioids as contributing to falls in elders[15].

Opioid tolerance develops rapidly following administration, even in the acute pain setting; however, in most circumstances, rapid resolution of pain over 3 days following surgery helps to prevent drug tolerance from becoming a significant factor in the postoperative patient[15]. With chronic use of opioids, opioid receptors decrease in population, as well as possibly in excitability. This 'downregulation' of opioid receptors manifests as increasing doses of opioids needed to obtain the same effect, and is usually clinically noted as 'tolerance' to a drug. Unfortunately, in up to 30–40% of patients that chronically consume opioids, opioid-induced hyperalgesia occurs[11]. Minor medical procedures, such as immunizations, venopunctures or intravenous catheter insertions, are perceived as excruciating. Higher doses of opioids are often prescribed by well-intentioned clinicians, but are not helpful, and frequently cause a further pain sensitivity[11].

Tramadol

Tramadol is a centrally acting opioid, which is effective for moderate-severe pain and is being used for various acute and chronic pain scenarios[45]. Tramadol is a synthetic opioid and has local anaesthetic effect on peripheral nerves which was shown in clinic and laboratory studies[45,46]. Analgesia begins within 1h and starts to peak in 2h . It is rapidly and extensively ab-

sorbed after oral doses and is metabolized in the liver. It has been proposed that tramadol has a lidocaine-like mechanism of action, which involves voltage dependent sodium channels causing axonal blockade[46]. In patients with moderate postoperative pain, i.v. or i.m. tramadol is roughly equal in efficacy to meperidine or morphine; for severe acute pain, tramadol is less effective than morphine[47].

Tramadol and meperidine are equally effective in postoperative patient-controlled analgesia[47]. In epidural administration for pain after abdominal surgery, tramadol is more effective than bupivacaine but less effective than morphine[47]. Kapral et al., adding 100 mg tramadol to 40 ml mepivacaine 1% in axillary brachial plexus block, shown that tramadol prolongs the duration of sensory and motor block without causing any significant side effects, this can be given as an example to the peripheral action of tramadol which was mentioned above[48].

In current literature there is limited description of tramadol use for geriatric postoperative pain relief. Potential advantages of administering tramadol for postoperative pain, in elderly patients, include satisfactory analgesia, long duration of action and limited respiratory depressant effects[49,50]. Since seizures have been described with tramadol administration, concurrent use of monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants should be avoided[40]. Tramadol may cause dizziness and reduce the seizure threshold[40]. Dosages should be reduced for patients older than 75 years or for patients with renal or hepatic dysfunction[47].

Patient controlled analgesia

In a general sense, patient-controlled analgesia (PCA) refers to a process where patients can determine when and how much medication they receive, regardless of analgesic technique. However, the term is more commonly used to describe a method of pain relief which uses disposable or electronic infusion devices and allows patients to self-administer analgesic drugs. Patient-controlled analgesia (PCA) with i.v opioid and patient-controlled epidural analgesia (PCEA) with a local anaesthetic in combination with an opioid are indicated for moderate or very painful surgery and are the route of choice after major abdominal or thoracic surgery. However, these techniques have been inadequately evaluated in elderly patients[51].

One of the reasons of pain underestimation in elderly patients is that this age group is reluctant to request analgesia[14]. In this situation, PCA provides a continuous i.v titration of analgesic regimens. All common opioids have been used successfully for PCA, with morphine the most. Whichever opioid is chosen for PCA, knowledge of its pharmacology is prerequisite for setting the dosing variables of the PCA device. In the setting of renal impair-

ment, opioids that do not have active metabolites, such as fentanyl, are preferred for PCA[11].

In comparison with young patients, the elderly reported greater pain relief in response to a fixed dose of morphine[30]. Using PCA, they self-administer less opioid than young patients but report comparable pain relief[14]. It has also been demonstrated that cognitively intact older patients are quite capable of using a PCA, achieve similar reductions in pain and self-administer less overall opioid; however, they use the PCA for a longer duration compared with younger adults[11]. A Cochrane review concluded that PCA provided superior analgesia and improved patient satisfaction compared with other conventional methods of delivery[52]. A study compared PCA and i.m analgesics in elderly patients after major surgery[14]. The results showed that PCA presented significantly fewer major confusional episodes, fewer major pulmonary complications, improved analgesia and early mobilization without increased sedation[14].

One potential problem with PCA is the practice of patient-controlled analgesia (PCA) by proxy (the administration of an PCA bolus dose by someone other than the patient). PCA by proxy is of particular concern in older patients who are not cognitively intact and cannot reliably use PCA. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recommended PCA by nurse proxy be utilized only at those institutions where patient selection criteria and monitoring standards have been established[15]. Licht E et al., describe three challenges when attempting to manage pain via a PCA devices in hospitalized patients with cognitive impairment. The initial challenge involves making a determination the patient will be able to use the device appropriately. Assessing whether the PCA is being appropriately used constitutes the second challenge. Evidence that patients are using the device, no way guarantees that they are operating it correctly. The third challenge involves the timing of PCA discontinuation. PCA use in this population requires continual reassessment and documentation of its effectiveness. Cognitively impaired patients are at particular risk for delirium and any changes in mental status demand prompt attention[53].

Non-opiod analgesic agents

Non Steroidal Anti Inflammatory Drugs (NSAIDs)

NSAIDs are among the most commonly used pain medications in the elderly, because they provide effective rapid and sustained relief for mild to moderate pain[11]. These drugs exert their analgesic and anti-inflammatory effects by diminishing peripheral and/or central prostaglandin production through the inhibition of the COX enzyme. The COX enzyme exists in two forms: COX-1 and -2. These enzymes are

reversibly inactivated by nonselective NSAIDs. Nonselective NSAIDs enhance pain relief, induce opioid-sparing effects and may reduce opiate adverse effects such as urinary retention, nausea and vomiting[11]. A meta-analysis showed that NSAID reduce morphine requirements in patient controlled analgesia following major surgery along with a concomitant reduction in morphine-related nausea, vomiting and sedation[54]. Additionally, perioperative NSAID administration can provide pharmacological action (antipyretic and anti-inflammatory activity) that when used in combination with regional anesthesia may enhance patient satisfaction and quality of their recovery[55].

However, NSAIDs are associated with significant adverse effects, especially gastrointestinal and renal toxicity, which are particularly prevalent in the elderly. An age-related decrease in gastric bicarbonate secretion, blood flow, and mucosal function, as well as delayed gastric emptying time, all contribute to a loss of stomach protection and an increased risk of gastritis, ulcer formation, and gastrointestinal bleeding[56]. An age-related decline in renal blood flow, in functional renal mass, in glomerular filtration rate and in creatinine clearance, affect drug elimination by the kidneys[11].Therefore, the elderly depend more on prostacyclin-mediated renal afferent arteriolar vasodilatation to maintain glomerular blood flow. Because NSAIDs impair this compensatory mechanism, a further decrease in renal elimination of drugs occurs[54]. The possible consequences are delirium or other impaired cognitive function, decreased functional independence, depression, poorer clinical outcomes, as well as increased hospital length of stay, health care use and overall costs[11,54,56]. The cyclooxygenase-2 inhibitors (COX-2 inhibitors) were and are excellent choices for perioperative analgesia[11]. Their lack of effect on platelet function make them extremely useful during the pre- and post-operative phase, provided care is taken to avoid patients at risk for renal failure and those with severe ischemic[15].

An additional concern associated with NSAIDs is that the very anti-inflammatory effects that make them effective analgesics may adversely affect healing processes that require inflammation[11]. Such area is bone healing, including fractures and effectiveness of bone fusions in spine surgery. NSAID administration has been shown to inhibit osteogenic activity and fracture healing in animal models[11].

To date, NSAIDs as a class of medication have not been deemed inappropriate for use in the elderly population because of inadequate evidence, with 2 specific exceptions. Indomethacin has been labeled as inappropriate because of toxicity to the central nervous system, as well as phenylbutazone because of its risk of bone marrow suppression[56]. Current guidelines

call for judicious use of NSAIDs, especially in elderly patients, with low doses (dose reduction at 25% to 50%) and short-term therapy, as well as close monitoring of renal and gastrointestinal function, blood pressure, and fluid status during and immediately after therapy in all elderly patients[56].

Paracetamol

Paracetamol is a safe and effective analgesic in the management of post-operative mild to moderate pain and other acutely painful conditions[57]. Its antinociceptive (pain-relieving) activity is generally thought to be due to central prostaglandin; inhibition however, central COX-2 inhibition and descending serotonergic modulation may also contribute to its analgesic properties[11]. Paracetamol is rapidly and completely absorbed from the gastrointestinal tract and neither the rate nor the extent of absorption appears to be age-dependent[57]. Elderly patients present a reduction in paracetamol clearance[57]. Unlike NSAIDs, it has minimal peripheral COX enzyme inhibition. In patients with severe liver disease elimination half-life can be prolonged and a reduction in dose and duration is recommended[57]. A number of factors that increase the risk of hepatotoxicity have been identified, including chronic alcoholism, dosing in excess of 4 g day^{-1}, pre-existing liver disease, concomitant use of microsomal enzyme inducers and malnourishment[57]. Given the physiological changes characteristic of frailty, in particular malnourishment, frail older people may be more susceptible to the adverse effects of paracetamol than their healthy counterparts.

Paracetamol's opiate-sparing properties are well established in the postoperative setting[54]. Paracetamol reduces opioid consumption compared with placebo in a variety of postoperative settings including total hip replacement, total knee replacement, hysterectomy and tonsillectomy[11]. Despite consistent reduction in 24 h postoperative morphine consumption, no apparent reduction has been found in opioid-related side effects after major surgery[54].

There has been increasing interest in the use of routine paracetamol in patients with dementia, even in the absence of overt signs of pain. A randomized, placebo-controlled study of 25 nursing home residents with moderate to severe dementia found regular administration of paracetamol (3 times daily) resulted in increased social interaction, work-like behavior and self-talk[57]. It appears that the regular administration of paracetamol can reduce the sequel of untreated pain and improve functioning in patients with dementia, although an optimal dose has not yet been ascertained. Maybe the routine administration of paracetamol can be applied also to postoperative geriatric patients with dementia.

Anticonvulsants

Gabapentin is an anti-epileptic drug that has demonstrated analgesic effect in diabetic neuropathy, post-herpetic neuralgia, and neuropathic pain. Gabapentin does not bind to GABA A or GABA B receptor but to the alpha-2 delta subunit of the presynaptic voltage gated-calcium channels. The inhibition of calcium release prevents the release of excitatory neurotransmitters involved in the pain pathways. Most of the studies of gabapentin (and occasionally its structural analog pregabalin) in the perioperative setting have been published in the last 8 years, and several systematic reviews available[58].Gabapentin and its successor pregabalin proved to decrease perioperative pain and limit long-term wound hypersensitivity[11]. This latter property is particularly important with those surgeries that have high rates of chronic wound pain: mastectomy, hysterectomy, inguinal hernia repair and thoracotomy. All of these types of surgery involve cutting peripheral nerves and inducing wound hypersensitivity[11]. Most of the reviews and meta-analyses concur that perioperative gabapentin helps to produce a significant opioid-sparing effect and probably improves postoperative pain score relative to control group[58]. Gabapentin and similar drugs seem to have a strong potential for perioperative use as an analgesic adjuvant and anti-hyperalgesic agent when used in conjunction with opioids[58].

Adverse effects associated with perioperative administration of the gabapentinoids are infrequent. An increased incidence of sedation and a trend towards more patient dizziness may limit their use in the ambulatory surgical setting. Gabapentinoids are not metabolized prior to renal elimination; therefore, dose adjustments are required for patients with renal insufficiency[11]. The choice of anticonvulsants for the treatment of acute pain in the elderly will depend on further research.

N-methyl-D-aspartate Receptor Antagonists (NMDA)

NMDA receptor antagonists and specifically ketamine, which commonly used in clinical practice, have been used in perioperative pain management of elderly patients[59]. Routes of ketamine administration include intravenous, subcutaneous, epidural, transdermal, and intra-articular. At low sub anesthetic doses (0.15–1 mg/kg), ketamine exerts a specific NMDA blockade and, hence, modulates central sensitization induced both by the incision and tissue damage and by perioperative analgesics such as opioids[58]. Subanesthetic ketamine dosing was found to lower pain scores, reduce morphine consumption and shorten postoperative i.v PCA dependence in orthopedic patients with malignancy[11]. There is a definite role of ketamine in preventing opioid-induced hyperalgesia in patients receiving high doses of opioid for their postoperative pain relief[58]. However,

clinical use of ketamine can be limited due to psychotomimetic adverse effects such as hallucinations and bad dreams. Other common adverse effects are dizziness, blurred vision, nausea and vomiting[11]. Clinicians concern over ketamine's side effect profile has limited its use, however, low-dose ketamine can be safely used, in elderly patients[11].

Other agents

Incorporation of antidepressant medications into perioperative pain management also has advantages that compliment analgesic techniques used in the elderly. In addition to their value as an analgesic, antidepressants improve a patient's sense of well-being, reduces fatigue, and do not disrupt the normal sleep cycle[55]. Certain antidepressants (treatment of neuropathic pain characterized by damage/dysfunction of CNS and/or PNS) have become popular as a non-opioid medication in the treatment of postoperative pain as a multimodal component in combination with regional anesthesia[55]. Anxiolytics can be included in a multimodal perioperative pain management regimen. Pain can cause anxiety and, in turn, anxiety often exacerbates the perception of pain. Therefore, anxiolytics may provide a mechanism to break this cycle and indirectly help to relieve pain, in elderly patients, in combination with regional anesthesia/analgesia[55].

Other non-opioid analgesic adjuvants that can be used for postoparerative pain relief, are clonidine, dexmetomidine, neostigmine and adenosine[58].Further research is necessary to establish their clinical efficacy in geriatric surgical population.

CONCLUSION

In our days, pain care providers have a variety of choices of analgesic pharmacotherapy and techniques to choose from, in order to provide adequate postoperative pain relief for the geriatric surgical patient. However, many factors should be taken into account before deciding on the type of pain therapy, such as the physiological changes of aging, the drug dosing, the drug toxicity, the altered pain perception, the need to individualize pain assessment tools and the frequent incidences of depression and altered cognition on painful states. Perhaps the greatest challenge of postoperative pain management in the elderly is the education of clinicians on the need to adjust their approach to pain management, in this special population. Pain management therapy, including multimodal analgesia, along with regional anesthesia, may help reduce the risk of negative influences in the elderly patient. Analgesic techniques that provide optimal pain control and low side effect profiles with minimal opioid exposure should always be considered for elderly patients and especially for cognitively impaired patients. Improvements in analgesic efficacy

with regional anesthesia may attenuate pathophysiological surgical responses, reduce the length of hospitalization, and accelerate patient rehabilitation and recovery. Careful monitoring and frequent assessment remain a priority. Confusional states often develop insidiously in elders following surgery, and frequently is undetected without careful assessment. Additionally, performing minimal invasive surgery can decrease surgical stress, the need for analgesics and contributes to early mobilization, alimentation and to reduced mortality in the geriatric surgical population.

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