Timely post-operative pain management in elderly patients is critically important. Given their physiological changes and comorbidities, management in this group of patients is different from the rest of the population. Knowledge of potentially inappropriate medications (Beers criteria) is relevant because of the presence of comorbidities in this population. Although acetaminophen continues to be safe, non-steroidal anti-inflammatory agents produce several adverse effects which need to be considered before they are used. On the other hand, opioids continue to be one of the pillars in analgesia, with due consideration of their adverse affects and interactions, and the need for dose adjustments. Adequate postoperative pain management prevents adverse effects and the risk of developing chronic pain.

Key words: Aged; Acute pain; Pain, postoperative; Chronic pain; Analgesics; Renal insufficiency, chronic; Heart failure; Anesthesiology.
INTRODUCTION

The number of older adults and their healthcare demands increase day by day. According to WHO data (1), the proportion of individuals over the age of 65 in the general population was 13.5% in 2017 and is estimated that it will reach 21.4% by 2050 (2).

In tandem with this demographic change there will be an increased demand for surgical services, because a significant number of elderly patients will undergo either urgent or elective procedures (2,3). Patients 65 and older account for the largest proportion of the surgical burden, specifically as it relates to cardiothoracic procedures, general surgery, ophthalmology, orthopedics and urology (4).

Two scenarios can occur when it comes to pain management and treatment in this population: under or over treatment with analgesics. The former results in poorly controlled pain, delirium, increased hospital length of stay or higher predisposition to develop chronic pain; the latter results in sedation, falls, drug-induced delirium, and urinary retention, among other complications (5). Although the occurrence of these complications is generally associated with the aging process, it develops differently in each individual, rendering the management of acute postoperative pain complex in these patients (6).

Pain assessment in this population is challenging, particularly in patients with advanced dementia, creating the need to use tools that can provide objective information about this symptom. Among these tools, the Pain Assessment in Advanced Dementia (PAINAD) scale as well as the Visual Description Scale (VDS) have been found to be reliable and valid for assessing pain in patients with dementia (7). On the other hand, the Visual Analog Scale (VAS) or the Numeric Rating Scale (NRS) can be used to assess elderly patients with no cognitive impairment, bearing in mind that patients of advanced age may appear more stoic and less willing to spontaneously express the intensity of their pain (8).

The objective of this narrative review is to discuss the approach to acute and postoperative pain in older patients from a practical perspective and based on the current evidence.

DEFINITION OF THE PROBLEM

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (9). It is worth highlighting that pain sensation and transmission change with age; notwithstanding, these changes do not result in diminished central pain perception (10). For this reason, the incidence of pain in general, and of perioperative pain in particular, varies depending on the age group (11).

Poor postoperative pain modulation has been described in the elderly (12-14). In a cohort study carried out in Denver, Colorado, in more than 300 patients over the age of 65 (15), the incidence of severe perioperative pain ranged between 62% and 87%. The study also found that pain intensity within the first 24 hours postoperatively was the main predictor of dissatisfaction with care (15).

PHARMACOKINETIC CHANGES ASSOCIATED WITH AGING

Absorption

Reduced absorption of drugs that require active transport mechanisms, (16) and lower gastric pH, results in impaired absorption of certain medications. Specifically for analgesics, few alterations are described in this phase (16).

Distribution

Distribution is determined mainly by distribution volume and protein binding. Physiologically, the total body water proportion diminishes in the elderly and there is an increase in fat mass percentage. This alters the distribution volume of multiple drugs (increasing the half-life time of lipophilic drugs such as diazepam and lidocaine, and reducing the half-life of water-soluble drugs such as acetaminophen and morphine). Additionally, age-related albumin reduction may increase the free fractions of large number of drugs and upregulate α1-acid glycoprotein expression, resulting in a higher possibility of adverse drug-related reactions (17).

Metabolism

With aging, hepatic flow and clearance, and the number of functional hepatocytes diminish, resulting in less effective oxidation and cytochrome-related processes. For that reason, older individuals may need more time to metabolize the same dose of a drug (17).

Clearance

This is a process that can happen through the kidney, the biliary tract or through the feces. However, it is worth noting that the physiological drop in glomerular filtration rate (GFR) due to aging may slow the clearance of certain drugs, requiring adjustments to the dose and frequency of administration. Morphine is one of such drugs, and it must be avoided in patients with a GFR of less than 60 mL/kg/min due to potential metabolite accumulation (16). Similarly, for tramadol, the American Geriatric Society (AGS) recommends adjustments when GFR is lower than 30 mL/kg/min (16); and as far as gabapentinoids are concerned, the recommendation is to reduce the dose of pregabalin and gabapentin when the GFR is lower than 60 mL/kg/min (16).

PHARMACODYNAMIC CHANGES ASSOCIATED WITH AGING

Some of the inherent characteristics of aging modify the direct action of the drug
in the body (pharmacodynamics), enhancing or diminishing its potential effect, thus creating the risk of a higher proportion of adverse reactions [16]. The dose and required adjustments of the main analgesic drugs that could be used in the management of postoperative pain in the elderly population are described below.

**Acetaminophen**

This central cyclooxygenase inhibitor has been shown to reduce the incidence of postoperative delirium and opioid requirements in the elderly [18]. It is usually well tolerated and there is no need to reduce the dose in patients with heart failure [19]. However, it is contraindicated in moderate-to-severe liver disease [20]. Liver toxicity in people without liver impairment has been described following an oral dose of more than 150 mg/kg/day. Nonetheless, in very frail patients (or patients weighing less than 50 kg), lower doses and/or longer administration intervals may be appropriate. In this population, the recommendation is to use a maximum oral dose of 60 mg/kg/day, which is equivalent in some patients to 1 g three times a day [21].

For venous administration, although the safety data sheet specifies a maximum dose of 4 g in 24 hours, it provides more detailed dosing instructions in terms of weight. It also includes a recommendation for a maximum adjusted daily dose in people with low body weight and/or risk factors for liver disease, heart, pulmonary or renal failure, concomitant administration of liver enzyme-inducing drugs, hepatitis, or chronic alcohol consumption [21].

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

These drugs inhibit prostaglandin production [22] and their analgesic and opioid-sparing action has been well documented [20]. Their adverse effects are far more frequent among the elderly due to diminished organ reserve in this population, hence the higher probability of drug-related acute renal failure in this age group [23]. As for gastrointestinal bleeding, its incidence is almost twice as high in the elderly as compared with younger patients [24] and as far as cardiovascular risk is concerned (acute myocardial infarction/stroke), it increases with the use of any NSAID, even when administered for a short period of time [25]. Therefore, in cases of GFR lower than 60 mL/min the use of NSAIDs during the postoperative period is contraindicated [26]. In contrast, topical administration has been shown to be as effective as the oral dose, with an incidence of adverse effects similar to placebo. Therefore, it is an option recommended in patients with localized pain [27].

All of the medications included in this group must be used cautiously in cases of severe liver disease and of heart failure. In cases of heart failure, they can cause fluid retention and decompensation and, therefore, they should be avoided. Should there be no other option, the dose must be reduced (25-50%) or the administration interval increased [19,22].

Below are examples of NSAIDs and their dosing in patients without comorbidities:

- **Diclofenac**: The recommended oral dose is 50 mg every 8 hours, maximum 150 mg/day, and 75 mg every 12 hours for intravenous administration [19].

- **Ibuprofen**: The recommended oral dose ranges between 200-2400 mg/day and it is advisable to use 200-400 mg every 4 to 5 hours [19].

- **Celecoxib**: The recommended oral dose ranges between 100-400 mg/day, i.e., 200 mg every 12-24 hours [19].

**Opioids**

These drugs are endogenous opioid receptor agonists. Because of physiological changes these drugs tend to be more potent and longer-acting, leading to a higher risk of adverse events [8]. Patient-controlled analgesia has been found to be a safe to use these drugs, but it is only recommended in elderly individuals with acute severe pain who have intact cognitive function [28].

Below are examples of the recommended doses for the most commonly used opioids:

- **Morphine**: It is recommended to administer an initial intravenous dose of 1.5-2.5 mg every 4 hours because age does not affect the pharmacokinetics of the drug. However, the recommendation is to reduce the dose by 25%, 50% and 75% in patients with stage 3, 4, and 5 chronic renal disease (CKD), respectively [29].

- **Hydromorphone**: It is recommended to initiate with an intravenous dose of 0.2-1 mg every 4-6 hours, given that age does not affect the pharmacokinetics of the drug. However, in moderate/severe liver or kidney failure, the dose should be reduced by 25-50% (creatinine (Cr) < 30 mL/min and Child Pugh B) [19,29]. It is important to remember that the drug is readily cleared in patients on hemodialysis, with a 60% reduction over the predialysis dose, thus requiring dose adjustments [29].

Dual-action opioids (tapentadol and tramadol) potentially reduce the incidence of opioid-related adverse effects; however, a 25-50% dose reduction is recommended in elderly patients compared to young adults for the management of acute pain [22]. As the number of comorbidities and of drugs used in the elderly (selective serotonin and noradrenaline re-uptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants) increase, these patients are at a higher risk of developing serotonin syndrome with the concomitant use of these types of opioids. Therefore, they must be used with caution [30].

**Gabapentinoids (gabapentin and pregabalin)**

These drugs bind to voltage-dependent calcium channels, resulting in inhibition and reduced release of excitatory neuro-
transmitters (31). Their use in acute postoperative pain is supported by the American Pain Society (32), and their benefits have been shown in the elderly population (33) because postoperative administration may reduce the incidence of chronic pain (34). The most significant adverse effects described are dizziness and drowsiness, which are more intense initially and are dose-related, thus increasing the possibility of falls and neurological involvement in this age group (22). It is important to bear in mind the synergistic relationship between their central adverse effects and those of opioids, which results in higher rates of respiratory depression (35). This group of medications must be used cautiously in the elderly, particularly in cases of renal impairment (22). The recommended doses are as follows:

- Gabapentin: The recommended oral dose ranges between 300 and 1,800 mg/day, with a maximum of 3,600 mg/day. The dose must be titrated every 1-3 days (19). In patients with renal failure, the recommended dose adjustments are as follows: for Cr ≤ 15 mL/min, 100-300 mg every 24 hours; Cr 15-29 mL/min, 200-700 mg every 24 hours; Cr 30-59 mL/min, 400-1400 mg/day divided into 2 doses; for patients on hemodialysis, dose supplementation may be required (19). No dose adjustment is required in case of liver or heart failure (19).

- Pregabalin: The usual oral dose is 150 mg every 8-12 hours and, if needed, the recommendation is to double the dose every 3-7 days, up to a maximum of 600 mg/day. In patients with renal failure, the recommended dose adjustments are as follows: Cr ≤ 15 mL/min, 25-75 mg/day; Cr 15-30 mL/min, 50-150 mg/day; Cr 30-60 mL/min, 75-300 mg/day. No dose adjustment is required in cases of liver or heart failure. However, to improve tolerance in elderly patients, low initial doses should be used (19).

Clonidine

This α-2 receptor agonist has not been shown to have analgesic effect in the elderly population. On the contrary, because of its mechanism of action, it increases the possibility of adverse cardiovascular effects (22) and can cause hypotension when used perioperatively (36). However, if utilized, dosing should be as follows:

If systolic blood pressure is > 100 mmHg, heart rate > 50 bpm, or if the RASS (Richmond Agitation-Sedation Scale) score is −2 or greater, a 75 μg oral dose is recommended, administered at 8-9 a.m. and 8-9 p.m. (37). Likewise, it must be used cautiously in cases of recent acute myocardial infarction, severe coronary heart disease, cerebrovascular disease and in the elderly population, because these patients can be more sensitive to sedative effects (19).

Ketamine

Its analgesic effect is due to NMDA-receptor blockade (22). In continuous infusion, it has been shown to improve pain control and reduce the need for opioids in the elderly population (38,39). Adverse effects include night terrors, confusion, hallucinations and fear (22). However, there is no clinical evidence of increased sensitivity to the adverse effects of this drug in the elderly (39). Given the above, the use of ketamine infusion is acceptable but not so bolus administration because of a higher incidence of adverse effects (22). The recommended intravenous dose is 2-7 µg/kg/min. Because it is cleared through the kidneys, it must be avoided in severe CKD and adjusted in cases of moderate CKD. No dose adjustment is required in cases of liver or heart failure (19).

Lidocaine

Produces hyperpolarization and reduces the excitability of postsynaptic spinal dorsal horn neurons (38,39). It has also been shown to exert an anti-inflammatorny and anti-hyperalgesic effect (40) especially in elderly patients undergoing abdominal, cardiac, orthopedic, urinary or endoscopic surgery, within the first 24 hours postoperatively (41).

Given lower liver blood flow levels in elderly patients, lidocaine clearance may drop by 30-40%; therefore, reducing the dose or infusion time appears to be reasonable (42,43). In general terms, perioperative administration of a 1 mg/kg bolus followed by an infusion of 1.5 mg/kg/hour for 48 hours is recommended (41,44).

Liver or cardiac failure are expected to reduce lidocaine clearance. However, this does not preempt the use of this drug, although longer infusion times of more than 60 minutes are foreseen. The infusion rate should be slower at the beginning and then increased (45).

**POTENTIALLY INAPPROPRIATE MEDICATIONS**

In view of the above, the potentially inappropriate medication (PIM) (46) concept was developed to designate medications whose potential risks (including adverse reactions or drug-drug interactions) override the desired effect in elderly patients. Several societies have developed criteria to help identify PIMs using either implicit or explicit strategies. Implicit strategies refer to those that identify potential PIMs supported by individualized judgement and clinical interpretation of each prescription, as is the case of the ARMOR (47) or the POM (48) strategies, which share common features such as the identification of potential adverse reactions and interactions. However, bearing in mind that the average elderly patient takes at least three medications, this analysis can be time consuming. Consequently, use of explicit strategies is recommended (46) as they are based on detailed lists which are regularly updated and can serve as teaching tools to encourage clinicians to stop and take time to think about the risks and benefits of certain medications before prescribing them, or to monitor carefully for potential adverse reactions (46). In this way, they can be used as prescription guidelines in...
elderly patients. Explicit strategies include the STOPP-START criteria (49), an initiative originating in Ireland in 2008 and recently updated in 2015, which has been embraced by the European Geriatric Medicine Society, with high applicability in hospitalized patients. However, this initiative includes multiple medications available in the European Union but which are not readily available in our setting. The Beers criteria already mentioned, developed by the AGS, are an explicit strategy developed in the United States, updated in 2008, 2015 and 2019. They allow to identify PIMs and third, the interaction subclassifications. Highlights include, first, the reference to analgesics classified as high risk in the elderly; second, the description of the medications that entail a higher risk depending on the underlying condition; and third, the interaction subclassifications.

It is worth noting that these recommendations are not a “straight jacket” but rather a means to render the prescription process easier, allowing for a more stringent analysis in search for the best option for the individual patient. Given their ease of application, the availability of the list of medications in our setting, and its recent update, the 2019 Beers criteria will be analyzed from the perspective of analgesic prescriptions in the elderly (50).

In this revision, medications are presented first by sections according to their potential risk and pharmacological interactions. Highlights include, first, the reference to analgesics classified as high risk in the elderly patients. Second, the description of the medications that entail a higher risk depending on the underlying condition; and third, the interaction subclassifications.

Table 1 summarizes these indications with a focus on analgesic and adjunct medications.

**Table 1. Indications focused on analgesic and adjunct medications.**

<table>
<thead>
<tr>
<th>High risk analgesics</th>
<th>Indications and considerations</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short and long-acting benzodiazepines (BZD)</td>
<td>- Elderly patients have heightened sensitivity and reduced long-acting BZD metabolism. - All BZDs increase the risk of cognitive decline, delirium, falls, fractures and automobile accidents in the elderly. - May be appropriate for periprocedural anesthesia, but not for perioperative pain management.</td>
<td>No indication in perioperative analgesic management in elderly patients. No indication in perioperative analgesic management in elderly patients.</td>
</tr>
<tr>
<td>Meperidine</td>
<td>May be associated with a higher risk of neurotoxicity, including delirium.</td>
<td>Its use in elderly patients must be avoided. Its use in elderly patients must be avoided.</td>
</tr>
<tr>
<td>NSAIDs in general</td>
<td>- Increase the risk of gastrointestinal (GI) bleeding or peptic ulcer in high risk patients (&gt;75 years, steroids, anticoagulants or anti-platelet agents). - Peptic ulcers, profuse GI bleeding or perforations caused by NSAIDs occur in 1% of patients treated for 3-6 months, and in 2-4% of patients treated for 1 year. - May cause blood pressure rises and induce renal injury (dose-dependent effect).</td>
<td>Avoid chronic use, unless other options are ineffective and provided the patient is able to receive gastric protection (proton pump inhibitors). Although this measure reduces the risk of GI bleeding, it does not eliminate it.</td>
</tr>
<tr>
<td>Indomethacin and ketorolac (IV or PO)</td>
<td>- Increase the risk of GI bleeding and peptic ulcer disease. - Increase acute kidney injury (AKI) in the elderly. - Among NSAIDs, indomethacin is associated with the highest odds of adverse events in the elderly, particularly in the central nervous system (CNS).</td>
<td>Avoid their use in elderly patients.</td>
</tr>
<tr>
<td>Skeletal muscle relaxants (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol)</td>
<td>Most of them are poorly tolerated in the elderly due to their anticholinergic effects, with potential adverse CNS effects.</td>
<td>Avoid their use in elderly patients. Avoid their use in elderly patients.</td>
</tr>
</tbody>
</table>

**Source:** Authors.

**USE OF ANALGESICS IN MULTIMORBID PATIENTS**

Given the growing prevalence of chronic diseases, the management of elderly patients with multimorbidity has become a source of concern for health systems (51). In Colombia, according to the 2015 National Study on Health, Wellbeing and Aging (SABE), a descriptive population-based study that included 23,694 Colombian adults over 60 years of age coming from rural and urban areas from all over the country, found that 84.8% of the population suffered from more than one chronic health condition (multimorbidity) (52). Accordingly, the relationship between the most common comorbidities and analgesic medications in the elderly is described below.
Heart failure

NSAIDs and COX-2 inhibitors should be used cautiously in controlled patients given the possibility of exacerbation, and they should be avoided in patients with acute heart failure. The possibility of adverse effects from COX-2 inhibitors is low, while it is moderate with the use of non-selected NSAIDs (50).

Opioids + benzodiazepines

Higher overdose risk with both medications (50).

Opioids + gabapentin or pregabalin

Higher risk of serious sedation-related adverse events such as respiratory depression and death. In this case, the recommendation is to avoid these medications, except when they are used in the management of opioid transition or as opioid-sparing agents. Although the risk is the same, precautions must be taken (50).

NSAID + warfarin

Higher bleeding risk. Avoid whenever possible (50).

Delirium

All BZD and non-BZD hypnotic sedatives like zolpidem and eszopiclone are contraindicated due to the risk of delirium worsening (50).

History of falls or osteoporotic fractures

Avoid hypnotic sedatives and opioids beyond acute postoperative management (50).

Peptic ulcer

Aspirin at a dose of more than 325 mg/day or non-selective NSAIDs may exacerbate existing ulcers or cause new or additional ulcers. These drugs should be avoided unless other options are ineffective and provided the patient can receive a gastroprotective agent, i.e., proton pump inhibitor (50).

Chronic kidney disease (CKD)

In chronic kidney disease stage 4 or higher (GFR < 30 mL/min), NSAIDs (selective non-acetylated salicylates, non-COX and COX, oral and parenteral) may increase the risk of acute kidney injury and worsen renal impairment. The recommendation is to avoid them (50).

Finally, below is a description of the pharmacological interactions that should be avoided at any rate in the elderly because of their potential associated risks, according to the 2019 Beers criteria (50).

Regarding local anesthetics, 0.05-0.15% bupivacaine concentrations have adequate characteristics for optimum balance between pain relief and adverse effects such as motor block and orthostatic hypotension (8). As for epidural opioids, fat-soluble agents (fentanyl, sufentanil) have rapid onset of action and short duration, making them a more rational choice than morphine (8).

REGIONAL ANESTHESIA/ANALGESIA

Regional anesthesia is becoming more common in patients of advanced age as an important component of multimodal enhanced recovery protocols after surgery. The aim is to reduce costs, improve safety and enhance the patient’s subjective experience during and after hospitalization. The use of these techniques has been shown to diminish the need for central-acting drugs such as opioids or systemic anesthetic agents, during and after surgery. This results in improved pain management, hemodynamic stability, faster recovery, less pharmacological interactions and less adverse effects from systemic medications (53). This management alternative should be considered in particular when neuroaxial techniques are contraindicated because of anatomic considerations, anticoagulation, the existing injury, or neuronal comorbidities affecting the spine (53).

Peripheral blocks for lower limb surgery, such as adductor canal block, are advantageous because of improved pain control, early mobilization and shorter hospital length of stay (53). Elderly patients usually require procedures involving the chest wall, such as pacemaker implantation or generator exchange, rib fractures or cancer resection. Studies have shown that combined pectoral nerve block I and II and single-injection thoracic paravertebral blocks for pacemakers and mammary and axillary dissection are clinically effective (53).

As far as abdominal surgeries in the elderly are concerned, they are also effectively covered by transversus abdominis plane (TAP) and rectus sheath
blocks and catheters (53). In turn, the quadratus lumborum block is of greater extension and longer duration than TAP blocks. However, it entails a greater risk of weakening the quadriceps muscle, thus increasing the risk of postoperative falls and bleeding complications, apart from requiring greater technical skills (53). Erector spinae plane (ESP) catheters have been used in cardiothoracic surgery with sternotomy (53).

Therefore, regional anesthesia/analgesia techniques reduce the risk of postoperative delirium and cognitive impairment, as well as hospitalization, and lead to faster rehabilitation and recovery. Additionally, they may reduce myocardial stress and the incidence of myocardial infarction and venous thromboembolism (deep vein thrombosis and pulmonary embolism) (53).

CONCLUSIONS

The population pyramid has changed notably in recent years. As a result, surgical interventions are performed in individuals of advanced age, requiring adequate and precise pain control during the perioperative period. Given the presence of multimorbidity as well as pharmacokinetic and pharmacodynamic changes in this population, special attention must be paid to the dose and the type of analgesic medication to be used, bearing in mind the risk of adverse events. A timely and practical approach is the use of the Beers criteria—updated in 2019—which suggest the medications that should be avoided. Additionally, it is important to know kidney and liver function before administering any analgesic, in order to reduce potential adverse events as much as possible.

It is worth noting that postoperative pain continues to be one of the most common complications described in surgery. When it is severe, it is associated with a higher unanticipated readmission rate, prolonged hospital length of stay, potential chronic pain development and chronic pain exacerbations. Therefore, adequate pain management is essential, and regional anesthesia/analgesia offers excellent and prolonged postoperative pain relief, improving patient mobility, reducing the need for opioids, and helping with physical therapy interventions. It has also been found to help with faster return to normal activities (54).

The type of surgical procedure must also be taken into account when selecting the analgesic technique. After major thoracoabdominal surgery, PCA and PCEA are considered the gold standard for pain management. In contrast, after limb surgery, nerve blocks appear to be the most appropriate strategy (8).

Finally, it is worth remembering that high multimorbidity in elderly patients requires an adequate therapeutic regimen in order to avoid worsening of their chronic conditions and diminish drug-drug interactions, thus enhancing optimum perioperative treatment in this population.

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