Review Article

Procedural sedation analgesia in the elderly patient

ABSTRACT

Elderly patients are perceived as a high-risk group for procedural sedation. Procedural sedation analgesia (PSA) is generally safe in older adults. What is not acceptable is undertreating pain or inadequately sedating a stable patient. All the usual precautions should be taken. One should consider any comorbidities that could make the patient more at risk of adverse reactions or complications. Older patients may be at higher risk for oxygen desaturation, but they usually respond quickly to supplemental oxygen. Geriatric patients usually require lower doses of medications. They tend to be more sensitive to medications, with slower metabolism, less physiologic reserve to handle side effects, and a smaller volume of distribution. The use of drugs for sedation in elderly patients requires careful consideration of their age-related changes in physiology and pharmacokinetics. The choice of drug should be based on the patient's medical condition, comorbidities, and potential adverse effects. Moreover, the administration should be done by trained personnel with close monitoring of vital signs and level of consciousness to prevent complications such as respiratory depression.

Key words: Analgesia, elderly, geriatrics, moderate sedation, PSA

Introduction

Procedural sedation analgesia (PSA) can safely be administered to the elderly population. The definition of elderly is a subjective term. That is, each patient should be considered an individual person with different physiologic and psychologic needs. Special attention must be given to ensure a safe environment for the induction of sedation in the elderly patient. The patient should be fully assessed, considering the physiologic changes that accompany aging. Elderly patients have an increased variability of drug response and decreased requirements for most anesthetic drugs. Elderly patients have an increased redosing interval. Continuous monitoring for signs of intolerance and cautious administration of sedation will help reduce the risks associated with sedation in the elderly.[1] With increasing age, the incidence of both benign and malignant gastrointestinal (GI) disease rises. Endoscopic procedures are commonly performed in elderly and very elderly patients to diagnose and treat GI disorders. There are many issues to contemplate when considering performing an endoscopic procedure on an elderly patient, including the anticipated benefits of endoscopy and the increased risks associated with procedural sedation and some endoscopic procedures.[2] This review will be in two parts. The first part will be an overview of PSA, and the second part will focus on the pharmacology of the most commonly used drugs in PSA.

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PSA overview

PSA is produced by the administration of pharmacologic agents, by a route that results in a depressed level of consciousness, but allows the patient to independently maintain a patent airway and respond appropriately to verbal commands or physical stimulus. Sedation occurs on a continuum from minimal sedation to general anesthesia, and patients progress along that line based on the medication given, the route, the dose, and the patient's own current clinical status. The provider caring for the patient must be able to recognize the clinical differences between the levels of sedation and be able to rescue the patient, should the patient progress to a deeper level than was intended. For example, the healthcare provider who is capable of monitoring or administering moderate sedation must be able to recognize when the patient has slipped into deep sedation and provide any necessary emergency care. This care may include airway support, fluids, more frequent assessments, or an immediate consult with an anesthesia provider or other practitioner with advanced airway skills, if necessary. The sedation continuum was first coined in 1985.[3] Being a subjective-based continuum, it has been recently formulated to include some objective columns to predict the ongoing risks of serious adverse events.[4] However, we sought to modify the current sedation continuum to make it more self-explanatory. Our modification included defining a level that we called the deeper sedation level. Furthermore, we added the drug-induced raw at the bottom of the original table of the sedation continuum. The reason for adding the drug-induced raw is to bring a close focus to the so-called endoscopist-directed propofol practice, which induces a deep sedation level on the continuum; however, with a little increase in the propofol dose the patient can easily be introduced to a deeper level on the continuum.[5] We believe that the "modified sedation continuum" adds a new dimension to the paradigm of defining different levels of sedation, which indefinitely will help physicians' providers to distinguish between deep and deeper sedation levels and hence interfere timely and properly earlier to rescue the patient before any serious adverse events happen. For better performance and understanding of the moderate sedation protocol, a course using a combination of didactic and simulation education is essential. For this purpose of course, we sought to develop a road map or what we call the "moderate sedation ladder," which summarizes the four essential steps of moderate sedation practice. The ladder is similar to the World Health Organization (WHO) analgesic ladder, but with different contents.[6] We believe that understanding the modified sedation continuum will enable providers with a clear distinction between different levels of sedation and hence proper titration of the induced drugs to avoid serious adverse events with reference to elderly patients. Equally, the summation of different issues of the moderate sedation ladder will help providers not to miss any step of the moderate sedation protocol. An anesthetist-led service is ideal but is a scarce resource. Safe protocols and sedation guidelines are beyond the scope of this review because these have been covered extensively elsewhere.[7] Nonetheless, it is mandatory to emphasize that if anesthetists cannot provide a service, then others will need training, support, and monitoring, ideally from the local anesthetic department. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recognizes the risks involved with sedation and analgesia for procedures and mandates that sedation practices throughout an institution be monitored and evaluated by the department of anesthesia. The American Society of Anesthesiologists (ASA) has responded to this challenging responsibility by developing practice guidelines for non-anesthesiologists who provide sedation and analgesia. Standard monitoring of heart rate, blood pressure, and arterial oxygen saturation during endoscopy is recommended by current guidelines on procedural sedation. The current ASA guidelines recommend the use of capnography in any patient undergoing moderate sedation. Capnography is an excellent tool for the early detection of hypoxemia and apnea in patients undergoing sedation for GI endoscopy.[8] The Integrated Pulmonary Index® (IPI) is an algorithm using parameters measured by capnography, such as partial pressure end-tidal carbon dioxide (PetCO2) and respiratory rate, as well as parameters measured by pulse oximetry, such as heart rate and arterial oxygen saturation (SpO2). Therefore, it combines the benefits of ventilation monitoring and oxygenation monitoring and could be a simple and handy device to monitor patients during sedation. IPI delivers a score from 1 to 10 that is supposed to help the medical team evaluate the patient's respiratory status by looking at a single parameter only. Values of 7–10 reflect stable parameters, whereas values below 7 require attention.[9]

There is an increasing number of elderly patients who undergo diagnostic bronchoscopy and GI endoscopic procedures under sedation and local anesthesia. Although PSA for endoscopic procedures improves patient comfort, there is a risk of oversedation in elderly patients. Only a few studies have evaluated the efficacy and safety of sedation for endoscopic procedures in elderly patients. Practitioners providing PSA should have a thorough knowledge of the pharmacology of the agents used. The potential adverse effects of these agents on airway patency, respiratory function, and hemodynamic balance should be fully appreciated. Adverse events during procedural sedation may be prevented by the appropriate pre-sedation evaluation of the patient, intraprocedural monitoring of physiologic function, and early intervention

when adverse effects are recognized. In the following section, we are going to discuss some of the drugs used in PSA that are suitable for elderly patients.

Drugs used in PSA

Given the continued increase in the complexity of invasive and noninvasive procedures, healthcare practitioners are faced with a larger number of patients requiring procedural sedation. Effective sedation and analgesia during procedures not only provide relief of suffering, but also frequently facilitate the successful and timely completion of the procedure. However, any of the agents used for sedation and/or analgesia may result in adverse effects. These adverse effects most often affect upper airway patency, ventilatory function, or the cardiovascular system. The pharmacology of the most commonly used agents for PSA and the outlines of their primary effects on respiratory and cardiovascular function will be mentioned in this part. Suggested guidelines for the avoidance of adverse effects through appropriate pre-sedation evaluation, early identification of changes in respiratory and cardiovascular function, and their treatment are outlined. Effective sedation and analgesia during procedures not only provide humanitarian relief of suffering, but also frequently facilitate successful and timely completion of the procedure. Adverse effects on hemodynamic and/or respiratory function may occur whenever sedative and analgesic agents are administered. It is important to note that no agent is completely devoid of the potential for life-threatening effects on respiratory and hemodynamic function. The occurrence of such problems and their impact on physiologic function can be lessened by the appropriate pre-sedation evaluation of patients, the monitoring of physiologic functions during sedation, and early intervention should problems arise.[10] The number of noninvasive and minimally invasive procedures performed outside of the operating room has grown exponentially over the last several decades. Sedation, analgesia, or both may be needed for many of these interventional or diagnostic procedures. Individualized care is important when determining whether a patient requires PSA. The patient might need an antianxiety drug, pain medicine, immobilization, simple reassurance, or a combination of these interventions. Some procedures are painful, and others are painless. Therefore, the goals of PSA vary widely. Sedation management can range from minimal sedation, to the extent of minimal anesthesia. PSA in the emergency department (ED) usually requires combinations of multiple agents to reach the desired effects of analgesia plus anxiolysis. However, moderate sedation, deep sedation, minimal anesthesia, and conventional general anesthesia can be all utilized for the management of GI endoscopy.[11] Many GI endoscopic procedures such as diagnostic gastro-duodenoscopy or screening colonoscopy are commonly performed in elderly patients. With the aging of the population and the development of digestive endoscopy technology, the number of elderly patients undergoing GI endoscopic procedures is increasing year by year. Although it is a noninvasive procedure, it usually causes obvious discomfort in the majority of patients, including nausea, vomiting, anxiety, or pain. Procedural sedation during GI endoscopy not only alleviates patients' anxiety, pain, and discomfort but also provides a comfortable environment for endoscopists throughout the procedure. Despite procedural sedation being generally considered safe in most patients, elderly patients undergoing procedural sedation are associated with a higher risk of hemodynamic instability, respiratory depression, and delayed discharge time, especially in those with cardiopulmonary disease conditions. Therefore, it is very important for elderly patients to choose safe and effective anesthetics during gastroscopy.[12]

Benzodiazepines

Benzodiazepines are a class of drugs that act on the central nervous system to produce sedation, anxiolysis, and muscle relaxation. They are commonly used in elderly patients due to their rapid onset and short duration of action. However, benzodiazepines can cause cognitive impairment, confusion, falls, and respiratory depression in elderly population. Therefore, they should be used with caution and at lower doses than younger adults. Benzodiazepines bind to receptor sites in the GABA system, increasing the efficacy of the interaction between GABA, its receptor, and the chloride channel. Midazolam is the benzodiazepine most frequently used for procedural sedation. It is a short-acting, water-soluble agent, which provides reliable anxiolysis, sedation, and amnesia. Of clinical note, the benzodiazepines as a group provide no analgesia, and so are often coadministered with opioids, generally fentanyl, because of their similar pharmacokinetic profiles (rapid onset and offset), which are desirable during PSA. Benzodiazepine metabolism occurs via hepatic oxidation and glucuronidation with the potential prolongation of their effects in patients with hepatic dysfunction. Effective sedation with midazolam can be provided by multiple routes of administration including oral, intranasal, rectal, intramuscular, and intravenous delivery. The benzodiazepines can have adverse effects on respiratory and hemodynamic function. These effects occur in a dose-dependent fashion and are modified by comorbid diseases and the synergistic effect of coadministration with other sedative or analgesic agents such as opioids. When midazolam is coadministered with an opioid, the sedation plan should include titration to effect, especially in elderly patients beginning with a lower dose of midazolam (0.05 mg/kg). Other clinically significant adverse effects include paradoxical excitement, which may occur in

up to 10–15% of patients.[13] These effects can be particularly alarming to family members and staff, as they are completely opposite in nature to the desired and expected results.

In a retrospective study, the records of 210 patients who underwent diagnostic bronchoscopy were analyzed. PSA was achieved with midazolam sedation at National Hospital Organization Omuta National Hospital between June 2017 and October 2019. Patients were administered 1 mg midazolam following 10 mL 4% lidocaine inhalation. When sedation was insufficient, 0.5 mg midazolam was administered additionally. Diagnostic yield, incidence of complications, amount of oxygen supplementation, decreases in percutaneous oxygen saturation (SpO2), changes in blood pressure, and degree of comfort were analyzed. Patients were divided into the elderly (n = 102) and non-elderly (n = 108) groups. No significant differences were observed in diagnostic yield and procedure time between the two groups, and no severe adverse events were noted in the elderly group. The degree of comfort during bronchoscopy was significantly higher in the elderly group. In patients administered <2 mg midazolam, the amount of oxygen supplementation and decreases in SpO2 were significantly smaller in the elderly group compared with the non-elderly group. The risk of adverse events related to midazolam sedation in bronchoscopy does not increase with age, and sedation improves comfort during flexible bronchoscopy in elderly patients. Moreover, a total dose of midazolam <2 mg is safe for elderly patients undergoing bronchoscopy.[14] A study has revealed that midazolam administration increases the risk of postoperative cognitive dysfunction (POCD) in elderly patients.[15] POCD is going to be discussed in detail in some review articles in this special issue on geriatric anesthesia.

Remimazolam

Remimazolam is a short-acting benzodiazepine that is used for sedation and anesthesia. It was developed by PAION AG, a German pharmaceutical company, and was approved for use in Japan in 2019. Remimazolam works by enhancing the activity of gamma-aminobutyric acid (GABA), a neurotransmitter that inhibits the activity of neurons in the brain. This leads to sedation, relaxation, and reduced anxiety. Remimazolam undergoes dose-independent ester hydrolysis. In the clinical doses, the enzymes are unlikely to be saturated, and as a result, there is no accumulation reported. In other words, the rate of reaction continues to follow first-order kinetics and is unlikely to change to zero order in the recommended doses. As a result, increasing doses or prolonged infusions are unlikely to have prolonged or residual effects. Due to organ-independent elimination, it can be safely used in elderly patients with hepatic or renal impairment.[16] In one study, it was shown that compared with propofol, the incidence of respiratory depression and other sedation-related adverse events caused by remimazolam are significantly lower and it is a suitable alternative sedative agent for elderly patients undergoing gastroscopy due to its non-inferior efficacy and higher safety profile.[17] In another study, it was shown that the rates of hypotension, bradycardia, and respiratory suppression were lower in elderly patients receiving remimazolam versus propofol on a fentanyl background for upper GI endoscopic procedure.[18]

Propofol

Propofol is a sedative or amnestic agent, possesses no analgesic properties, and should be combined with an opioid or ketamine preferably with ketamine (commonly known as "ketofol") when analgesia is required. Ketamine–propofol combination is attractive because of the opposing hemodynamic and respiratory effects of these two agents. The anesthetic induction dose of propofol in healthy adults ranges from 1.5 to 3 mg/kg b.w. with recommended maintenance infusion rates varying from 50 to 200 μg/kg/min (3–6 mg/kg/h), depending on the depth of sedation that is required. Following intravenous administration, propofol is rapidly cleared from the central compartment and undergoes hepatic metabolism to inactive water-soluble metabolites, which are then renally cleared. Its rapid redistribution, clearance, and metabolism provide rapid awakening when the infusion is discontinued. Rapid arousal and quick return to baseline behavior allow for early discharge following outpatient procedures. Propofol slightly affects POCD. It is well established that moderate sedation results in a high level of both patient and physician satisfaction and may also improve the quality of upper GI endoscopy. Data on combined sedation with midazolam or propofol for GI endoscopic procedures in elderly patients are very rare. In a retrospective analysis of midazolam or propofol sedation during 454 endoscopic procedures in 347 patients ≥70 years with high-level comorbidity reflected by a 28-day mortality rate of 2.9% and an ASA score of class III or higher, the authors found no procedure-associated mortality or major side effects. In comparison with patients of younger age, elderly patients needed lower propofol doses with few minor complications.[19]

Dexmedetomidine

Dexmedetomidine is an α2 adrenergic agonist with beneficial sedative properties and a limited adverse effect profile. Dexmedetomidine causes its physiologic effects by activation of specific transmembrane α2 adrenergic receptors at various locations throughout the Central Nervous System. These effects include sedation, anxiolysis, and analgesia. Hypertension has also been reported during the loading dose. This hemodynamic effect is thought to be mediated via peripheral α2B adrenergic agonist

leading to vasoconstriction before the onset of the central effects. Bradycardia appears to be more common when dexmedetomidine is coadministered with other medications that have negative chronotropic effects.[20] Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced endoscopic procedure and requires deep sedation. Deep sedation with dexmedetomidine for the respiratory drive preserved has become popular in recent years. However, the use of dexmedetomidine in elderly patients is controversial because its adverse events are more common. In one study that investigated the effectiveness of a single loading dose of dexmedetomidine combined with propofol for deep sedation of ERCP in elderly patients, it was found that the combination reduced propofol consumption and artificial airway intervention and provided better hemodynamic stability than propofol alone for deep sedation in elderly patients during ERCP.[21]

In one study, it was found that patients who received dexmedetomidine sedation supplement for peripheral nerve block were associated with a lower incidence of postoperative delirium (POD) and early POCD compared with propofol sedation. Sedation with dexmedetomidine also facilitated patients to be out of bed and discharged early after surgery.[22]

Ketamine

While ketamine has become a favorite agent in many PSA procedures and has been used successfully in children for many years, it is probably not the best first choice in certain older adults.

- There are several older, small studies of ketamine used as the sole agent in the OR to perform open reduction and intern fixations of hip fractures in older adults.[23] In a study with an average patient age of 83 years, during ketamine administration, patients experienced increased blood pressure and cardiac index, but there were no serious adverse events.[24] Another small study compared ketamine and propofol as the sole agents during hip fracture repair in the operation room and found that ketamine increased myocardial oxygen demand.[25]
- In general, there is a higher prevalence of hypertension and coronary artery disease among older patients. Increasing the myocardial oxygen demand could present a risk with ketamine use. However, there is little evidence that ketofol may be a good option (combination of propofol and ketamine), but the recent studies of ketofol in the ED enrolled a few older patients.[26]

Opioids

Fentanyl is a rapidly acting opioid (at doses between 1 and 2 ug/kg) often coadministered for pain control during PSA. Unfortunately, fentanyl possesses respiratory depressant effects that may be additive with those of propofol when these agents are used in combination. The elderly patient requires fewer doses for pain relief. Morphine clearance is decreased in the elderly patient. Sufentanil, alfentanil, and fentanyl are twice as potent in the elderly patient, due to an increase in brain sensitivity to opioids with age. There are changes in the pharmacokinetics and pharmacodynamics of remifentanil, which is more potent in geriatric patients. Clearance and the volume of the central compartment decrease with age, and the infusion rates should be titrated.[27] Fentanyl is a short-acting opioid with high potency and minimal cardiovascular effects. This agent has a rapid onset of action, usually within 2 minutes, and the duration of action is 30–40 minutes. The serum half-life is approximately 90 minutes. This combination of rapid onset, high potency, and short half-life makes fentanyl an excellent agent for most PSA procedures in the ED. The usual required dose is between 2 and 3 μg/kg by slow IV push given in increments of 0.5–1 μg/kg every 2 minutes to a maximum of 5 μg/kg for both adults and children. The total amount of the agent required is dependent on the individual's response. Because of its high potency, safety, and relatively short half-life, fentanyl is very easy to titrate using multiple small doses to achieve the desired effect, especially in elderly patients. Fentanyl can induce severe respiratory depression, especially when used with other agents such as midazolam. This side effect is dose-related and usually appears within 5 minutes of administration of the agent. The doses used for PSA in the ED have not been reported to cause muscular and glottic rigidity or "board chest," which has been well documented when the agent is used in anesthetic doses. General pruritus is usually not present with the use of fentanyl as occurs with many opioids as it does not cause histamine release, and nausea is usually minimal when compared to other opioid analgesics.[28]

Reversal agents

Both benzodiazepines and narcotics have reversal agents that if used correctly could save an over-sedated patient from having a respiratory arrest. Flumazenil antagonizes the action of benzodiazepines on the central nervous system and inhibits activity at GABA or benzodiazepine receptor sites. It is contraindicated in patients with serious tricyclic overdoses. Available in injectable 0.1 mg/mL, flumazenil can be given undiluted or in 5% dextrose in water, lactated Ringer's solution, or 0.9% normal saline. The initial dose is 0.2–0.4 mg IV over 15 seconds. If ineffective, a second dose can be given every 60 seconds. The maximum initial dose is 1.0 mg. If the patient becomes over-sedated, an additional dose can be given and a drip may need to be started because the

half-life of the offending benzodiazepine may be longer than the half-life of flumazenil, whose half-life is 40–80 minutes. Adverse effects include seizures, dizziness, headache, blurred vision, diplopia, visual field deficit, hyperventilation, nausea, and vomiting.

Naloxone hydrochloride is a pure narcotic antagonist. It reverses the respiratory depression, sedation, and hypotensive effects of opioids. In the absence of narcotics, naloxone has no activity. Caution needs to be used in narcotic addiction, cardiac disease, and use of cardiotoxic drugs. The rapid reversal of narcotic depression may also cause nausea, vomiting, diaphoresis, and circulatory stress. The initial dose is 1–2 mg IV at 2- to 3-minute intervals until reaching the desired effect of reversal. It can be given undiluted as a bolus or as an IV infusion with 5% dextrose in water or 0.9% normal saline. As with flumazenil, a drip may need to be started due to the longer half-life of the offending agent. Naloxone has a half-life of 30–81 minutes. Adverse effects include seizures, ventricular tachycardia, ventricular fibrillation, acute narcotic abstinence syndrome, and return of pain.[29]

In summary, PSA is generally safe in older adults. What is not acceptable is undertreating pain or inadequately sedating a stable patient. All the usual precautions should be taken. One should consider any comorbidities that could make the patient more at risk of adverse reactions or complications. Older patients may be at higher risk for oxygen desaturation, but they usually respond quickly to supplemental oxygen. Geriatric patients usually require lower doses of medications. They tend to be more sensitive to medications, with slower metabolism, less physiologic reserve to handle side effects, and a smaller volume of distribution. The use of drugs for sedation in elderly patients requires careful consideration of their age-related changes in physiology and pharmacokinetics. The choice of drug should be based on the patient's medical condition, comorbidities, and potential adverse effects. Moreover, the administration should be done by trained personnel with close monitoring of vital signs and level of consciousness to prevent complications such as respiratory depression.

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Conflicts of interest

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