
Management Strategies in the Postoperative Course, with Particular Attention to Pain Treatment: Revision of the Most Recent Knowledge

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The postoperative period is a crucial time for patients. Careful monitoring, integrated with a treatment plan that takes into account the basal pathologies and postoperative peculiarities of specific interventions (surgical site, blood losses, pain intensity, hospitalization duration), is able to reduce the complications and, thus, postoperative morbidity and hospital stay. Recent guidelines on perioperative treatment emphasize the role of simultaneous therapeutic measures, ensuring safe risk-management pathways such as prevention of surgical site infections, thromboembolic prophylaxis, strategies to reduce the incidence of perioperative stroke, and strategies to ensure enhanced techniques integrating postoperative analgesia, nausea and vomiting control, early mobilization, and enteral nutrition [1, 2]. The main integrated recommendations below are derived from the guidelines on the treatment of postoperative pain, characterized by levels of evidence A and B [3–7].

7.1 Postoperative Pain

The technique of analgesia adapted to the individual patient plays a key role in the evaluation and management of perioperative pain. Pain must be considered as the fifth vital sign, after heart rate, blood pressure, temperature, and urine output. These vital signs must be periodically evaluated, measured, and transcribed in the clinic database (level A). The evaluation must include not only the pain at rest but also, and especially, the pain “incident” using one of the following scales: numeric rating scale, visual analog scale, or verbal rating scale.

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A good model of postoperative pain management must take into account the following parameters:

- (a) patient characteristics;
- (b) type of surgery and surgical technique;
- (c) intensity and duration of postoperative pain and its tendency to become chronic;
- (d) organization of existing resources and control through the adoption of tools to “measure” and “assess” pain at rest and during movement;
- (e) identification and training of personnel involved.
- (f) the process should be sensitive to the clinical context of application

In its 2012 guidelines, the American Society of Anesthesiologists [5] emphasized the role of outcome patient monitoring and of a dedicated service for acute pain management.

The Acute Pain Service (APS) formally is multidisciplinary, involving anesthesiologists, surgeons, nurses, physiotherapists, and other specialists. There is not a single best organizational model, but it must to be adapted to the local environment and its possibilities. The APS improves pain control in surgical wards and seems able to reduce adverse effects such as nausea and postoperative vomiting.

It is recommended to refer to the quality indicators (level C) and to consider the following key points when organizing an APS:

1. institutionalization of the service with identification of a responsible person and the employees (staff assigned);
2. organization for the care of patients during nights and weekends;
3. identification of an referent 24-h anesthesiologist;
4. sharing, drafting, and updating of written treatment protocols;
5. systematic survey of pain;
6. collection of data on the efficacy and adverse effects of the protocols used;
7. carrying out an audit at least annually;
8. continuing education.

In its guidelines, the American Society of Anesthesiologists [5, 6] also stressed the concept of multimodal analgesia with the use of different classes of drugs: COX-2 selective, NSAIDs, acetaminophen, Calcium channel alpha-2-delta antagonists (pregabalin, gabapentin). Drugs must be administered at fixed times, the blocks locoregional with local anesthetics considered as part of a multimodal approach. The regime must optimize the therapeutic efficacy and reduce the risk of adverse events. The choice of drug, administration route, and duration of therapy should be individualized.

7.2 Systemic Analgesia

Paracetamol has a good analgesic efficacy (NNT for 3.5–3.8 500–1,000 mg) with no significant effects side (Level A). Monitoring of the liver is necessary when paracetamol is used. Its pharmacological profile is not altered in the presence of

alterations of the renal function (Level B). The association of paracetamol and morphine reduces the daily consumption of opioid by a variable percentage of 33–20 % (Level A). The administration of acetaminophen and tramadol is more effective than paracetamol – codeine (Level B).

NSAIDs (nonsteroidal anti-inflammatory drugs) are effective drugs for the pain of average intensity. In combination with opioid analgesics they reduce the need for analgesia and are able to control moderate to severe pain (Level A).

The *COXIBs* are contraindicated in patients with ischemic heart disease and/or cerebrovascular disease, congestive heart failure, and aorto-coronary bypass (Level B).

Opioids are the drugs of choice for the treatment of moderate to severe POP postoperative pain (Level A). Their epidural, intrathecal, and intravenous (IV) patient-controlled analgesia (PCA) use is preferred over intramuscular injections at fixed hours.

The use of opioids can cause adverse effects in a dose-dependent manner. The use by continuous infusion device may increase the side effects. Vomiting can be reduced with the use of droperidol, dexamethasone, ondansetron, or propofol at minimal doses, thus avoiding nitrous oxide (Level C).

Tramadol results in less respiratory depression than morphine (Level B). Its association with morphine is not recommended for an infra-additive effect (Level C). A better association is with NSAIDs (Level D).

Remifentanyl is the opioid of choice for patients with kidney and liver disease (Level B), and for patients recovering in a protected ward environment.

Oxycodone is used in the DPO as analgesia step-down after use of IV PCA (Level D) or opioid premedication if a short half-life opioid is chosen for minor surgery.

Ketamine administered perioperatively can reduce the intensity of postoperative pain (Level A), the incidence of postoperative nausea and vomiting (PONV) (Level B), and morphine consumption by 30–50 % (Level A).

7.2.1 Epidural Analgesia

Epidural analgesia is recommended for the following reasons: In postoperative pain, it has an analgesic efficacy higher than systemic analgesia with opioids (Level A). With local anesthetics, associated with opioids, it can reduce respiratory complications, lung infections, and paralytic ileus (Level A). The association of thoracic epidural analgesia and early enteral nutrition is able to reduce protein catabolism postoperatively (Level C) and the incidence of peripheral thrombosis (Level C). The association between low doses of local anesthetic and lipophilic opioids represents the best compromise in terms of control of postoperative pain and reduced incidence of side effects (Level A). The risk of epidural hematoma is very low when the recommendations relating to the timing of thromboprophylaxis and the suspension of antiplatelet agents drugs are complied with. Spinal hematoma has an incidence of 0.02 % (Level D). In suspected epidural hematoma, it is necessary to request an urgent check with magnetic resonance imaging (MRI) or a computerized tomography (CT) scan (Level A). A decompression by surgical laminectomy within 6 h

Table 7.1 Drug, interventional and physical therapy

Intravenous route	Oral route	Rectal route	Subcutaneous route	Topical
Antiepileptic Ketamine NSAIDs Opioids	Antiepileptic Antidepressants Antihistamines Anxiolytics Cortisone Hypnotics Local anesthetics NSAIDs Opioids	Acetaminophen Aspirin Opioids Phenothiazines	Local anesthetics Opioids	Capsaicin Cold Hot Lidocaine/ prilocaine Local anesthetics
Interventional				
Treatment of pain with the use of local injections or invasive procedures				
Consultation preoperatively with a specialist in pain therapy				
Physical therapy				
Biofeedback				
Exercise				
Hot/cold				
Immobilization				
Massage				
TENS (transcutaneous electrical nerve stimulation)				
Relaxation				

after symptom onset can reduce neurological complications (Level E). The incidence of major neuraxial complications linked to the use of an epidural catheter to deliver postoperative analgesia is approximately 1:1,000. The incidence of epidural abscess is 0.07 % and is associated with high fever and infection site insertion. Early diagnosis is crucial. In most cases, the bacteria responsible are *Staphylococcus aureus* or *S. epidermidis*. The combination of infection of the insertion site and hyperpyrexia are sufficient to investigate with NMR nuclear magnetic resonance, and the addition of local pain or neurological symptoms imposes the need for urgent investigations (Level D). The average time from the insertion of the catheter to the first symptoms can vary from 1 to 60 days. The initial symptoms include back pain, fever, and leukocytosis (Level A) (Table 7.1).

7.2.2 Continuous Peripheral Blocks

In recent years, continuous peripheral blocks have been used successfully in the treatment of acute postoperative pain (Level A). After orthopedic surgery of the upper and lower limbs, clinical trials have shown that continuous peripheral blocks are as effective as continuous epidural block, and both are considerably more effective than parenteral opioids (Level A). Studies have shown a remarkable effectiveness of these techniques in reducing pain at rest and during movement, the consumption of opioid analgesics, and nausea and vomiting. This treatment has

improved, especially in orthopedic surgery, functional recovery with adequate analgesia, and reduced side effects (Level A). Regional analgesia should also be used in critically ill patients to reduce the consumption of sedatives and opiates (Level C).

After major orthopedic surgery of the upper and lower limbs, clinical studies have shown that continuous peripheral blocks are as effective as continuous epidural and that both are greatly *more effective than intravenous opioids or infiltration with local anesthetics* (Level A).

Regional analgesia also should be used in critically ill patients to reduce the consumption of sedatives and opiates (Level C).

It has been shown that, in knee surgery, the adductor canal ultrasound-guided block, compared with continuous femoral block, ensures equal analgesia and lower incidence of quadriceps femur motor block, thus preventing accidental falls in the first postoperative days [4, 8]. Likewise, the role of *continuous* thoracic paravertebral block for breast and thoracic surgery has been reaffirmed as an alternative to continuous epidural and TAP (transversus abdominis plane) block (abdominal wall block with continuous infusion of local anesthetic).

7.2.3 Infusion Modality

Several studies have shown that PCRA (*patient controlled regional anesthesia*) is a more effective infusion baseline in postoperative pain control and allows a better mobilization of the patient (Level C).

It is recommended to avoid continuous infusion techniques with no flow control devices and to adopt a programmed registration system, including pain level, analgesia effectiveness, and side effects notation (Level A).

7.2.4 Patient Controlled Analgesia (PCA)

7.2.4.1 PCA Intravenous

The intravenous PCA is a method for the treatment of postoperative pain that allows the patient to self-administer the needed doses of analgesics. The intravenous PCA opioid guarantees better analgesia (with an average of 5 mm on a scale 0–100 mm for pain) and greater patient satisfaction than conventional treatments with parenteral opioids at fixed hours (Level A).

The intravenous opioid PCA, however, is not associated with a reduction in opioid consumption or reduced incidence of side effects related to opioids compared with conventional treatments with parenteral opioids (Level A). There is no evidence that a basal infusion can improve pain relief or quality of sleep, or reduce the number of doses required by IV PCA. Before starting treatment with PCA, a correct initial titration must be made to reach an adequate level of analgesia.

The incidence of side effects related to opioids, including respiratory depression, is the same for both the IV PCA and the intermittent administration of opioid

analgesics (Level A). The risk factors for respiratory depression associated with IV PCA are divided into those associated with the patient (elderly, children, obesity, obstructive sleep apnea, respiratory failure) and those related to the technique:

- mistakes made by the patient
- errors made by operators (programming errors, accidental boluses during the syringe change, inappropriate prescription drug dose, inadequate dose interval).

7.2.5 Day Surgery

7.2.5.1 Anesthetic Approach (Level A)

Whenever possible, general anesthesia should be integrated with preemptive analgesia (acetaminophen/NSAIDs and/or peri-incisional local anesthetic infiltration).

Due to the expected vomiting/pain interactions, the use of nitrous oxide is not recommended. If indicated, peripheral nerve blocks are preferred over general anesthesia (Table 7.2).

7.2.5.2 Early and Late Postoperative Recovery: Analgesia at Discharge (Level D)

The hospital discharge letter must include pain assessment, postoperative drug provision plan, rescue dose commitment, and adverse events prevention suggestions. It is recommended to provide, both orally and in writing, information and clear and precise instructions on where and when prescribed drugs can be taken and how side effects can be controlled. These recommendations relate particularly to the need to clearly inform patients who are discharged with continuous perineurous infusion of local anesthetics, emphasizing the risks of loss of motor function and ambulation.

ENF 4 h
LMWH low doses 12 h
LMWH high doses 24 h
Fondaparinux 36 h
Anti Vitamin K INR <1.5
Ticlopidine 10 days
Clopidogrel 7 days
Tirofiban 8–10 h
Hirudin 8–10 h
Abciximab 24–48 h
Dabigatran Nc
Rivaroxaban 18–22 h
Apixaban 24 h

Table 7.2 Security intervals between drug administration interfering with coagulation and execution of epidural block

7.3 Specific Groups of Patients

7.3.1 Elderly Patients

In elderly patients (>65 years), the following is recommended:

- use of a simple semantic scale (absent, mild, moderate, severe) to measure pain in collaborating patients;
- use of neuro-behavioral parameter scales in uncooperative patients;
- taking account of changes in pharmacokinetics and pharmacodynamics to avoid the risks involved in the choice of NSAIDs/coxibs;
- reducing the minimum effective dose of opioids from 1/3 to 2/3;
- use of methods of PCA is safe in elderly patients without cognitive deficits;
- use of methods of epidural analgesia requires a reduction of the doses of local anesthetics and opioids;
- ensure a level of analgesia aimed at early motor rehabilitation and a complete functional recovery plan.

7.3.2 Pediatric Patients

An appropriate analgesia plan must be considered over sedation alone. The most used drugs for the procedural analgesia are nitrous oxide, associated or not to low doses of ketamine and midazolam. For minor procedures (venipuncture, stitches, etc.) the inhalation of nitrous oxide (50 %) and/or the use of topical local anesthetic can be considered an effective and safe procedure (Level A).

For procedures of moderate severity (lumbar puncture, aspiration of bone marrow) the inhalation of nitrous (50 %) and the use of topical or local anesthetic for injection is effective in most patients (Level A).

For other procedures (reduction of fracture), regional IV blocks with local anesthetic are effective in most of children, despite the potential complications and the high incidence of side effects. General anesthesia may be more appropriate in some groups of patients. Cognitive techniques, the presence of family members, behavioral interventions (Level C), and administration of sugar reduce behavioral responses in neonates and infants (Level B).

Paracetamol and NSAIDs are effective for pain with moderate intensity and reduce the opioid requirements after major surgery (Level A). Acetylsalicylic acid should be used with caution in children to reduce the potential risk of Reye's syndrome. In addition, aspirin and NSAIDs increase the risk of postoperative bleeding (Level A). Severe side effects are rare in children above 6 months of age.

Opioids are effective and can be used safely in children of all ages. The initial opioid dose must be established according to weight and age and must be adjusted according to the individual response.

The mode of administration with PCA is very effective and safe; it can be used in children who are able to collaborate, typically 5 years and older.

The caudal block is effective for analgesia after interventions on the lower abdomen, perineum, and lower limbs. Continuous epidural infusion is effective in controlling postoperative pain but requires the collaboration of an experienced team capable of accurate monitoring (cardiovascular and neurological) to identify early complications such as local anesthetic toxicity, more frequent in children due to reduced clearance, and lower protein binding from local anesthetics or intravascular drug injection, more frequent in children because of the low consistency of the sacral ligament. Continuous epidural infusion of local anaesthetics guarantees a level of analgesia equal to intravenous opioids, prolonged by adding clonidine (Level B).

In day surgery, wound infiltration with local anesthetic, caudal block, or peripheral perineural blocks (the dorsal penile nerve block for phimosis, ileoinguinal/ileo-hypogastric nerve block for hernia) provides suitable analgesia (Level B).

7.3.3 Obese Patients

Prolonged hospitalization is often necessary in obese patients to ensure that analgesia is both effective and safe, with close monitoring of the sedation level, respiratory rate, oximetry, and capnometry (Level B).

Frequently, OSA (obstructive sleep apnea) is a syndrome associated with obesity. In these patients, strict monitoring associated with reduction of opiate doses is mandatory. Remifentanyl seems to provide greater hemodynamic stability than sufentanil, although these differences vanish when used in TCI (target controlled infusion). The perioperative use of NSAIDs, ketorolac in continuous IV infusion during surgery and within 24 h, compared with the use of the same remifentanyl, has been shown to ensure a greater intraoperative hemodynamic stability, a faster discharge from the PACU (post-anesthesia care unit), and a better outcome. The use of the PCA mode and PCEA are recommended (Level C), even if epidural loco-regional analgesia (PCEA) shows more complications and technical difficulties [2].

7.3.4 Chronic Opioids Consumer Patients (CCO)

In these cases the following is recommended:

- preoperatively identify CCO patients;
- do not reduce the usual daily doses of opiates;
- identify a multimodal treatment plan, “proactive” vs postoperative pain;
- premedicate with opioids, titrating the dose;
- use, if possible, perioperative continuous techniques of regional anesthesia;
- administer NSAIDs and/or paracetamol at full doses daily;
- assure full daily doses of opiates (>2–3 times the average dose routinely used), possibly titrated using target controlled infusion (TCI) intraoperatively and PCA postoperatively;
- avoid both holes in analgesia and oversedation phases, planning for the transition to the oral route in the following days;

provide for the use of adjuvants perioperatively such as alpha-2-agonists, low-dose ketamine, even appealing the rotation of opioids from morphine/fentanyl versus methadone or buprenorphine.

7.3.5 Patients Suffering from Sleep Obstructive Apnea (OSA)

The prevalence of OSA is widely underestimated in adults (5 % undiagnosed, mild forms up to 20 %, moderate to severe forms in 7 % of cases).

In the setting of patients with OSA the following is recommended:

preoperative identification of patients at risk (COPD, smoking, chronic snorers, obese) and possible programming of postoperative hospitalization in a protected area; prefer opioid-sparing analgesic techniques; monitor the level of sedation, over the respiratory rate; supplement oxygen also by nasal C-PAP (continuous positive airway pressure); banish in these patients all forms of baseline opioids infusion; titrate drug administration by continuous epidural and IV PCA.

7.4 Treatment-Related Adverse Events in Postoperative Pain

When using anti-inflammatory drugs, any contraindications should always be ruled out (known allergy to NSAIDs, gastric or duodenal ulcer, thrombocytopenia, renal failure) and it is a good idea to associate gastro-protective drugs (H2 blockers or pump inhibitors).

When using local anesthetics, the possibility of neurotoxicity should be considered (alterations in the level of consciousness, agitation, seizures) and cardiotoxicity of substances (heart arrhythmias).

When using opioids, the following clinical signs should be monitored: nausea, vomiting, skin rash, itching, and blood pressure. Nursing staff should have adequate training to detect early clinical warning signs of possible complications:

clinical signs suggestive of allergy (skin rash, edema, appearance of macules, papules), bruising (indicators of poor platelet function); contraction diuresis (evaluate azotemia, creatinine).

When using opioids, the most common side effects and the simplest rules for its treatment are:

nausea and vomiting: use antiemetics, modify opioid dose or predict transition to alternative medication;

constipation: always provide a intestinal stimulation plan when using an opioid, avoid fiber-based laxatives to avoid production of gas and abdominal cramps;

itching: change opiate, eventually add antihistamine;

myoclonus: change opiate, use benzodiazepine to treat myoclonus;
respiratory depression: use naloxone 0.4 mg, administer 0.02 mg/min up to the reversion effect.

In patient-controlled analgesia, mistakes can relate to:

mixing drugs (concentration, dilution);
setting of the system (basal infusion, bolus dose, maximum hourly/day dose);
inadequate monitoring of vital signs (blood pressure, heart rate, respiratory rate, SaO₂, sedation level);
mismanagement of therapy if analgesia is not effective;
underestimation of the difficult patient.

7.4.1 Epidural Infusions

To identify the early appearance of clinical signs of complications, the following should be monitored every three hours: level of consciousness, blood pressure, heart rate, respiratory rate, sensory discrimination and motor block (dermatome level of analgesia), SaO₂, urine output, nausea, vomiting, and visual analog scale at rest and during movement.

The remote but devastating risks related to the use of the technique can be related to dislocation of the catheter and its migration to the subdural/intraspinal space, spinal cord ischemia, and spinal hematoma.

Opioids, as already said, may induce itching, nausea, vomiting, and respiratory depression and may cause loss of control of metameric sensorial discrimination, variability of respiratory rate, pulse oximetry, and end-tidal CO₂, or excessive drowsiness of the patient.

Local anesthetics can induce orthostatic hypotension and motor block which, in turn, could mask a compartmental syndrome (from any surgical hematoma in a closed space). In the presence of ineffective analgesia and in cases of suspected malfunction of epidural infusion, a series of tests must be performed in the ward:

- verify the normal flow of the epidural catheter;
- check the dressing and links;
- inject 5 ml of saline;
- call the anesthesiologist.

The events that should alert the attention of ward staff during the use of the infusion for epidural are:

- onset of respiratory depression (RR < 8/min);
- onset of motor block despite the use of local anesthetic at low concentrations or failure of regression of motor block after central blocks: call the anesthesiologist,

identify clinical warning signs of spinal hematoma, perform spinal MRI, proceed to neurosurgical evacuation within 3h – maximum 6 h – from the onset of symptoms.

It is important to respect the security intervals between last dose of antiplatelet/anticoagulants and execution of the central block. This emphasizes the importance of not suspending antiplatelet agents in patients at risk of clogging metallic coronary stents (30 days) and double antiplatelet therapy in patients with drug-eluting stents (365 days), but in these cases central blocks should be avoided.

7.4.2 Peripheral Blocks

Complications may be due to the appearance of:

- infection of the insertion site;
- hematoma in proximity of the block due to vascular injury;
- permanent or transitory nerve injuries;
- systemic toxic manifestations of the use of excessive anesthetic doses or its vascular reabsorption (early treatment with 20 % lipidic solution, administering a bolus of 100 ml, continuing with 400 ml in 20 min until full recovery);
- pneumothorax in thoracic blocks.

7.5 Chronicity of Surgical Acute Postoperative Pain (POP)

The risk of postoperative pain chronification can be reduced with minimally invasive surgical techniques and avoiding any direct cuts, inflammation, or scarring to peripheral nerves. Data in the literature on the effectiveness of preventive multimodal analgesia in reducing the chronicity of POP are conflicting.

Several studies have been conducted on the effectiveness of prevention with opioids, demonstrating its ineffectiveness. The most promising results are given by the use of anticonvulsants and multimodal drug plans using anticonvulsants, antidepressants, ketamine, local anesthetics, or any combination of these [7–12].

Postoperative chronic pain (persistent) occurs in 10–50 % of patients undergoing surgery, especially after hernioplasty, breast and thoracic surgery, and limb amputations. In 2–10 % of cases, the pain remaining after surgery is classified as severe. Genetic factors are probably involved because not all patients who suffer from a peripheral nerve injury develop chronic pain. The presence of infection and surgical bleeding, the appearance of compartment syndrome and breakage of internal organs favor the development of chronic pain.

7.6 Recent Knowledge

Despite the enormous progress that has been made in anesthetic practice in the last 50 years, the worldwide incidence of intraoperative mortality is estimated at nearly 30 deaths/million uses of anesthetics. A mortality of 20 % is estimated in postoperative critical patients, thus elevated to 50 % in patients with multi organ failure.

Diseases such as stroke, myocardial infarction, ARDS, renal failure, and acute intestinal ischemia are more frequent perioperatively. At the base of the organ damage is ischemic damage that triggers the activation of genes involved in production of inflammatory substances capable of worsening the stability of the membrane and thus increasing cell and tissue damage. There are perioperative strategies for reducing complication such as anemia, tachycardia, hypertension, and hyperthermia (Table 7.3).

Table 7.3 Perioperative treatments can change the postoperative outcome

Drug	Advantage postoperative	Level of evidence
Intraoperative normothermia	Reduced surgical site infection	Level A
Regional anesthesia	< surgical site infection	Level B
Avoid hyperglycemia	< surgical site infection	Level B
Using continuous insulin infusion	< surgical site infection	Level A
Regional anesthesia	< frequency of cancer recurrence	Level B
Avoid nitrous oxide	< frequency of cancer recurrence	Level C
Perioperative use of NSAIDs	< frequency of cancer recurrence	Level C
Perioperative use of Propofol	< frequency of cancer recurrence	Level C
Avoid heterologous transfusions	< frequency of cancer recurrence	Level C
Preoperative treatment with iron and erythropoietin	< transfusion	Level B
Intraoperative fluid restriction in cardiopulmonary bypass	< transfusion	Level C
Hypotensive anesthesia	< transfusion	Level B
Recovery intraoperative blood	< transfusion	Level A
Anesthesia with propofol	< transfusion	Level C
Antifibrinolytic agents	< transfusion	Level A
Epidural anesthesia pre-incisional	< incisional postoperative chronic pain development	Level C
Anesthesia without nitrous oxide	< incidence of perioperative myocardial infarct	Level B
Using beta blockers in surgery non-cardiac surgery	< postoperative cardiovascular complications	Level B
ALR use in children	< neurocognitive side effects of immature brain tissue	Level C
ALR use in the elderly	< long lasting postoperative cognitive dysfunction	Level C

Preoperatively, it is important to check for hyperlipidemia; use of beta blockers, statins, and antiplatelet agents puts patients at risk. Assess the patient carefully and determine which pharmacological treatment should be undertaken, continued, or integrated according to its pharmacokinetics and pharmacodynamics and its interference with the anesthetic technique used [13–15].

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