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## Low-opioid and opioid-free anesthesia - a review of current data

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**Introduction:** Opioids are one of the most frequently used drugs during anesthesia. Due to the side effects anesthesiologists try to limit their number during anesthesia. They use low-opioid and opioid-free anesthesia.

**Purpose:** The purpose of this work is to present the current state of knowledge and recent reports on low-opioid and non-opioid anesthesia and their use.

**Materials and Methods:** The search was conducted using PubMed and GoogleScholar databases. Articles were searched in English using the following keywords: "low-opioid anesthesia," "non-opioid anesthesia," "OFA," "LOA"

Key words: "low-opioid anesthesia", "non-opioid anesthesia", "OFA", "LOA", "anesthesiology", "opioids".

**Conclusion:** low-opioid anesthesia techniques are being used more and more frequently and reduce the incidence of opioid side effects: respiratory depression, postoperative nausea and vomiting. This helps ensure greater patient safety and shortens the postoperative recovery period.

**Abbreviations:** OFA - opioid free anesthesia, LOA - low opioid anesthesia, OBA - opioid based anesthesia

## **Introduction:**

Opioid analgesics have a well-established role in general anesthesia and in the perioperative period. They are used both by anesthesiologists administering anesthesia and by surgical physicians relieving pain in recovery rooms. Unfortunately, despite their high analgesic efficacy, their use is associated with a number of side effects including respiratory depression, excessive sedation, postoperative nausea and vomiting. [1] Low-opioid anesthesia is a concept involving general anesthesia with little or no opioids (*LOA - low opioid anesthesia*) or *opioid free anesthesia (OFA - opioid free anesthesia)* to protect the patient from the previously mentioned side effects, while providing the patient with a satisfactory level of intra- and postoperative analgesia. Non-opioid analgesics, e.g. metamizole, ketoprofen, paracetamol and so-called coanalgesics, e.g. dexmedetomidine, ketamine, dexamethasone, magnesium sulfate, lidocaine, clonidine, are used interchangeably. In addition to multidirectional pharmacotherapy, one cannot fail to mention the techniques of regional anesthesiology: epidural anesthesia and regional anesthesiology involving blocks of peripheral nervous system structures.

## **Side effects of opioids:**

Opioids (fentanyl, remifentanyl, sufentanyl) are still the most commonly used analgesics during general anesthesia. They are also the mainstay of postoperative care (oxycodone, tramadol, morphine). Anesthesiology textbooks, when discussing opioid agents and the purpose of their use, always mention:

- Reduce the need for anesthetics and supplement their effects
- effective analgesia
- postoperative pain management

Numerous side effects [2, 8] of drugs in this group are known:

- lethargy
- excessive sedation
- dizziness
- nausea
- vomiting
- constipation
- respiratory depression
- hypoventilation
- facial itching
- urinary retention
- slowing down of peristalsis, constipation
- increased muscle stiffness
- suppression of the cough reflex
- Throat muscle weakness (sleep apnea).

- hyperalgesia
- opioid tolerance

Hyperalgesia [3] is understood as an increased response to pain stimuli caused by exposure to opioids. The more fentanyl is given intraoperatively, the more the patient will need opioids in the postoperative period - he develops opioid tolerance. This is particularly marked in the case of remifentanyl. [4] One should also not forget about the immunomodulatory effect of opioids, which can have a negative impact on postoperative infections and tumorigenesis [5,6]. Nevertheless, stress and inadequate pain control can also contribute to cancer progression. [7] There is a study that shows no difference between anesthesia technique and breast tumor recurrence rates [12].

### **Coanalgesics:**

The analgesia of LOA and OFA is based on the concept of acting on multiple receptors, as none of these drugs alone can replace a conventional opioid. These drugs per se do not have an analgesic effect, but they help reduce the analgesic doses needed [11]. Anesthesia is based on a combination of multiple drugs: NMDA antagonists (ketamine, magnesium sulfate, lidocaine), sodium channel blockers (local anesthetics), anti-inflammatory drugs (metamizole, ketoprofen) steroids (dexamethasone), analgesics (paracetamol), alpha-2-agonists (dexmedetomidine, clonidine) and regional analgesia techniques, e.g. fascial blocks or regional anesthesia e.g. epidural catheters. Multimodal approaches block or alleviate pain transmission and transmission along inflammatory pathways at different levels, reducing (LOA) or eliminating (in the case of OFA) the need for opioids [11].

**Drugs:**

<b>Substance</b>	<b>Mechanism of action</b>	<b>Dosage according to PTBB recommendations [19].</b>
Lidocaine	It extinguishes foci of excitation in nerves damaged during surgery. Has anti-inflammatory effects by limiting the action of pro-inflammatory factors, reduces peripheral sensitization and hyperalgesia [13].	<ul style="list-style-type: none"> <li>- During induction of anesthesia - 1-1.5 mg/kg.</li> <li>- During the procedure, continuous i.v. infusion. 1-1.5 mg/kg/hr.</li> <li>- in the postoperative period (24-48 hrs) - 0.5-1.5 mg/minute</li> </ul>
Ketamine	Inhibits NMDA receptor activation. Has analgesic effects, inhibits activation of pro-inflammatory cytokines, and provides hemodynamic stability - activates the sympathetic nervous system [16].	<ul style="list-style-type: none"> <li>- Procedural procedures (&lt; 60 min); 0.1-0.3 mg/kg bolus i.v. during induction</li> <li>- surgical procedures (&gt; 60 min), with no scheduled i.v. infusion in the postoperative period; 0.1-0.3 mg/kg bolus i.v. during induction, followed by Boluses at a dose of 0.1-0.3 mg/kg every 30-60 minutes</li> </ul>
Dexmedetomidine	Acting on $\alpha_2$ receptors at the sinus site sedates the	- In premedication up to 30 min. intravenous

	patient. Inhibits the transmission of pain information from the operated site. [18]	infusion (5-10 min.), at a dose of 0.5-2 mcg/kg b.w. - Intraoperatively and/or postoperatively, intravenous infusion of 0.2-0.5 mcg/kg/hour.
Dexamethasone	It has anti-inflammatory, anti-emetic, anti-edema effects, inhibits the activation of pro-inflammatory cytokines, inhibits the activity of the Nerve fibers damaged during surgery. [17]	Dosage by intravenous route: 0.1-0.2 mg/ kg b.w. in a 10-15 minute intravenous infusion intraoperatively
Magnesium sulfate	It acts by blocking the NMDA receptor. Inhibits activation of pro-inflammatory cytokines [15].	- During induction for anesthesia - 30-50 mg/kg. - During the procedure, an infusion of 10-15mg/kg/hour. - In the postoperative period (24-48 hours) - 10-15 mg/kg/hr.
Clonidine	They inhibit the transmission of pain information from the operated structure [14].	- In premedication 30-90 min before surgery at a dose of 3-5 mcg/kg b.w. - Intraoperatively and/or postoperatively, intravenous infusion 0.2-0.3 mcg/kg/hour

### **Indications for LOA and OFA anesthesia [9]:**

- obese patients
- Patients with obstructive sleep apnea
- COPD patients
- opioid addicts
- Patients with developed opioid tolerance (oncology patients) [20].
- Patients undergoing surgery for oncological reasons [10,12].

### **Contraindications to LOA and OFA anesthesia: [13, 18]**

- Contraindications for NSAIDs: danger of aggravation of renal failure, aggravation in gastrointestinal bleeding (in combination with GCS); potential hepatotoxicity of paracetamol
- hypotension
- bradycardia
- hypovolemia
- defaults
- shock
- Allergies to drugs that are components of anesthesia

### **Anesthesia in practice according to Mulier [28]:**

Mulier in 2018 compared the effect of opioid and non-opioid anesthesia in laparoscopic bariatric surgery on a group of 50 patients. He proposed an OFA regimen that included supply:

Before induction:

- dexmedetomidine (0.5 mcg/kg)

- ketamine (0.25 mg/kg)
- lidocaine (1.5 mg/kg)

Induction:

- propofol
- rocuronium

Anesthesia maintenance:

- Lidocaine infusion (1.5-3 mg/kg/h)
- Dexmedetomidine infusion (0.25-1 mg/kg/h)
- sevoflurane

All drugs were dosed per ideal body weight (IBW) according to the Brock equation [28].

In the conventionally anesthetized group, patients received:

Before induction:

- sufentanyl 0.5 mg/kg

Induction:

- propofol
- rocuronium

Anesthesia maintenance:

- sufentanyl 0.25 - 1 mg/kg/hour

Monitoring patients in the recovery room yielded several conclusions:

- More frequent drops in saturation in patients undergoing anesthesia with opioids



- feelings of cold and body tremors were significantly higher in the group of patients anesthetized with opioids
- Patients in the OFA group required fewer boluses of morphine for postoperative pain relief
- Patients in the OFA group reported lower pain values on the VAS scale

### **Research on postoperative pain:**

In one study of patients undergoing laparoscopic cholecystectomy, 30 patients were given classical anesthesia with opioids, while 30 were given OFA. Patients in the OFA group were given dexamethasone and paracetamol before induction. Midazolam, lidocaine, propofol and rocuronium were used for induction. Subsequently, ketamine with lidocaine and magnesium sulfate were used in maintaining anesthesia. Postoperative pain was assessed on the VAS scale for 24 hours after surgery: at 1 h, 4 h, 8 h, 12 h and 24 hours. The group of conventionally anesthetized patients was statistically significantly more likely to have pain at 1 hour after surgery and at 24 hours. [22]

Another study evaluated 77 patients undergoing pancreatic resection and anesthetized with remifentanyl (42 patients) and OFA (35 patients). All patients received propofol, sevoflurane, dexamethasone, diclofenac and muscle relaxants. The OFA group additionally used dexmedetomidine, lidocaine and s-ketamine. It was shown that opioid consumption in the postoperative period and pain intensity were lower in the OFA group. Patients undergoing OFA anesthesia left the hospital an average of 4 days earlier (14 days vs. 10 days). There were no differences in operative time, blood loss, bradycardic episodes, use of vasopressors and time to extubation between the two groups. [23]

A study was conducted in China on a group of 101 patients undergoing laparoscopic radical colectomy under general anesthesia. A perianal block with ropivacaine was also performed. In the non-opioid anesthesia group,

dexmedetomidine was used. In the other group, remifentanyl/sufentanyl was used. The study showed no statistically significant differences in pain sensation (VAS scale). The incidence of postoperative nausea and vomiting was also not significantly different. [24]

A hysteroscopy procedure was performed on 90 patients. Lidocaine was administered in half of them, and sufentanyl in the other half. Other drugs were administered equally in both groups. The postoperative rate of PONV was checked, which was 21% in the group of patients not receiving opioids. PONV in the group with Sufentanyl was 41%. Moreover, the group of patients with lidocaine scored higher on the QoR-40 questionnaire, and were extubated faster. [25]

In Cameroon, 36 patients undergoing gynecological procedures under general anesthesia were evaluated. Eighteen of them were anesthetized with opioids, while the rest were anesthetized without opioids. Conventional anesthesia involved the administration of dexamethasone, diazepam, fentanyl, propofol, rocuronium and isoflurane. The second group used lidocaine, magnesium sulfate, ketamine, dexamethasone, propofol, rocuronium, and isoflurane and clonidine. It was shown that in the group of 18 patients anesthetized with the conventional method, 15 of them had postoperative constipation, while in the OFA group only 1. Postoperative nausea and vomiting were 9 vs. 2, respectively. The time from surgery to the first attempts to get out of bed was also measured. For low-opioid anesthesia, this was an average of 10.5 h, while the fentanyl-anesthetized group required twice as long. The QoR-40 questionnaire showed better satisfaction for patients anesthetized with OFA. [26]

**Advantages of LOA and OFA anesthesia:** [22, 23, 24, 25, 26]

- lower intensity of postoperative pain
- rarer percentage of PONV
- faster return of peristalsis after the procedure
- Faster "activation" of the patient after surgery

- shorter hospitalization of the patient

### **Conclusion:**

Low-opioid and non-opioid anesthesia techniques are being used more and more frequently and help reduce the incidence of opioid side effects: respiratory depression, postoperative nausea, vomiting and many others. They are also a very good alternative in the context of postoperative pain control. They also allow faster discharge of patients from the hospital, which is in line with the ERAS protocol [21].

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Conceptualization, writing, original draft preparation, writing review and editing, project administration- D.Cz-K.; AG; AD

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### **Conflicts of Interest**

The author declares no conflict of interest

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