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Review

OPIOID FREE GENERAL ANESTHESIA IN CLINICAL PRACTICE – A REVIEW ARTICLE

Sanja Sakan[1], Žana Turudić[1], Sanja Peremin[1], Andrej Šribar[1,2], Nataša Sojčić[1], Marcela Čučković[1], Domagoj Vergles[3] and Jasminka Peršec[1,2]

[1]Department of Anesthesiology, Resuscitation and Intensive Medicine, Dubrava University Hospital, Zagreb, Croatia;
[2]School of Dental Medicine, University of Zagreb, Zagreb, Croatia;
[3]Department of Surgery, Dubrava University Hospital, Zagreb, Croatia

SUMMARY – Currently, enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways with the goal to achieve early patient recovery after surgery with minimal postoperative complications. According to studies, opioid free general anesthesia has many perioperative benefits and should be part of the ERAS protocols in specific surgical and patient indications. Opioid free general anesthesia is a multimodal balanced technique that is based on the concept that opioids are not used preoperatively or intraoperatively until the patient has aroused. The basic concept of opioid free general anesthesia is intravenous administration of several nonopioid drugs that operate at different pharmacological sites blocking surgical stress and sympathetic activation response. Moreover, current studies have shown that opioid free anesthesia is a technique which satisfactorily controls postoperative pain as the fifth vital sign, and has minimal side effects and better patient recovery with the same surgical conditions as general multimodal balanced anesthesia. However, further research is needed.

Key words: *Acute pain; Multimodal anesthesia; Opioid free anesthesia; Perioperative period*

Introduction

Today in the anesthesiologist's practice, we mostly use multimodal balanced anesthesia and analgesia to achieve satisfactory pain relief and minimize the side effects of each drug we use, especially the opioids. The main goals of general anesthesia are to accomplish hypnosis, absence of movement and adequate anti-nociception, or in other words, intraoperative analgesia during surgical default[1]. Intraoperative analgesia or anti-nociception is the key parameter in everyday anesthesiologist's practice that cannot be adequately measured. From the anesthesiologist`s perspective, anti-nociception during anesthesia is measured through changes in circulatory variables such as blood pressure and heart rate under surgical default, and consumption of opioid analgesics during surgery and according to patient body weight[1]. So, we can conclude that intraoperative monitoring of blood pressure and heart rate changes is reflection of the sympathetic activation and parasympathetic deactivation play as an answer to surgical somatic default[1]. In the multimodal balanced general anesthesia and analgesia, we use the opioid and nonopioid analgesics to achieve the best anti-nociception effect and minimize the postoperative side effects, as well as to fasten patient recovery and return to normal everyday activities and work[2]. The concept

Correspondence to: *Sanja Sakan, MD, PhD*, Department of Anesthesiology, Resuscitation and Intensive Medicine, Dubrava University Hospital, Av. Gojka Šuška 12, HR-10000 Zagreb, Croatia
E-mail: sanja.sakan@hotmail.com

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of multimodal balanced anesthesia is based on the fact that many different transmitters are involved in the pain pathway (noradrenaline, adrenaline, serotonin, glutamate, gamma-aminobutyric acid, acetylcholine, N-methyl-D-aspartate, etc.)[1]. So, opioid analgesics can block only one transmitter in the pain pathway (enkephalins), and are not sufficient for the anti-nociception stability of patient during anesthesia and surgical default[1]. That is why in balanced multimodal general anesthesia we use nonopioid analgesics, peripheral and central nerve blocks with the aim to act on different transmitters at various sites of the pain ascending and descending autonomic pathways[3,4]. This complex mechanism of pain pathways and already noted postoperative opioid side effects have led to the consideration of skipping the use of opioid analgesics in the specific settings and the development of the opioid free anesthesia and analgesia concept.

Opioid Free General Anesthesia

Opioid free general anesthesia (OFA) is a multimodal balanced technique that is based on the concept that opioids are not used preoperatively or intraoperatively until the patient has aroused[2,5]. OFA without peripheral nerve blocks is possible by the intravenous administration of several nonopioid drugs that operate at different pharmacological sites blocking surgical stress and sympathetic activation response. Because there are no large randomized multicenter trials that could show benefits, minimal side effects and patient satisfaction of using OFA in everyday practice against multimodal balanced opioid anesthesia, it is recommended to utilize OFA only in specific indications presently. Therefore, specific absolute indications to avoid opioids and utilize OFA are obesity (body mass index >40 kg/m^2), obstructive sleep apnea syndrome (OSAS), and bariatric surgery[2,6]. Relative indications for OFA are positive history of postoperative nausea and vomiting (PONV) and intense postoperative pain, bewaring opioid induced tolerance and opioid induced hyperalgesia, oncologic surgery, laparoscopic surgery and patients with opioid prescriptions, chronic pain, and positive opioid addiction history[2,7,8]. Like every medal with two sides, OFA also has clinical contraindications. The contraindications for OFA are drug allergy, trauma surgery, renal and hepatic disease, uncontrolled arterial hypertension and hypotension, coronary artery disease, cardiomyopathy, atrioventricular conduction blocks, cerebrovascular damage, intracranial pathology, uncontrolled psychiatric disease, weak autonomic system, and the last one is patient refusal[2,6].

Mechanism of Action, Benefits and Side Effects of Nonopioid Analgesics in Opioid Free General Anesthesia

As in multimodal balanced opioid anesthesia, the main principle of action in OFA is to attain balance in the sympathetic and parasympathetic action activated by surgical or other noxious default. As already mentioned, in OFA we use different pharmacological drugs in small doses that act at various sites of the pain ascending and descending pathways and block different transmitters to achieve adequate anti-nociception. Dexmedetomidine is a central alpha-2-adrenergic agonist which binds to the G-protein and inhibits the L-type calcium channel[6,9]. It is not connected with significant respiratory depression, PONV, pruritus, constipation, ileus and delirium. Since it facilitates enhanced postoperative recovery, dexmedetomidine is considered as part of the enhanced recovery after surgery protocol. Bradycardia is a major limiting side effect of utilizing dexmedetomidine in OFA. However, it responds well to atropine[10]. Depending on the location of the receptors, it induces sedation if located in the locus coeruleus, or analgesia if located in the spinal cord. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist[9]. It provides analgesia at subanesthetic doses limited to 0.25 mg/kg bolus doses to prevent side effects such as tachycardia and hypertension, as well dysphoric syndrome with hallucinations[11,12]. At this dose, it is allowed to be used in patients with coronary artery disease. Moreover, ketamine is a very good nonopioid analgesic for treating neuropathic pain. Magnesium as analgesic performs as the NMDA receptor antagonist as well, but in a different way from ketamine[9]. It also performs analgesic effects by regulating calcium influx into the cells[9]. It is also a good adjuvant for neuropathic pain. The loading dose is 30-50 mg/kg followed by intravenous infusion of 10 mg/kg/h. The relevant side effects of magnesium are bradycardia and hypotension, which occur at higher doses than mentioned earlier. It is recommended to reduce intraoperative muscle relaxant and anesthetic drug doses when using intraoperative magnesium to prevent residual neuromuscular block and delayed emergence from anesthesia. Lidocaine is an amino acid local anesthetic which has good nonopioid analgesic effects[9]. It considerably decreases opioid requirements and has shown benefit in abdominal

surgery, hence its ability to diminish inflammation and cytokine effects in the intestines[13]. Besides, it is a good neuroprotective agent during anesthesia, which inhibits postoperative cognitive dysfunction[14]. It has many side effects such as perioral paresthesia, metallic taste, tinnitus, cardiac and neurological toxicity[15]. However, it is important to remember that in anesthesia, the only sign of lidocaine toxicity could be bradycardia and wide QRS complexes[16]. So, it is necessary to emphasize measurement of lidocaine plasma levels, especially in patients with liver dysfunction and low cardiac output states. Intravenous acetaminophen is a nonopioid adjuvant that has more potent analgesic action with faster onset and much higher plasma levels than oral form due to bypassing the first metabolism in the liver[17]. It also has antipyretic and weak anti-inflammatory effects[18]. Special attention should be paid to patients with liver disease and the maximal daily dose in these patients should be limited to 2 g/day[19]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are nonopioid drugs with significant analgesic action[20]. If used for several days, there is a risk of bleeding, renal impairment, gastritis, and peptic ulceration. Selective cyclooxygenase 2 inhibitors are not recommended for perioperative use due to a higher rate of thrombotic events, and should be avoided in patients with positive history of myocardial infarction, cerebrovascular and peripheral vascular disease[11]. NSAIDs should also be excluded in elderly patients with renal dysfunction. Gabapentin and pregabalin are derivatives of inhibitory neurotransmitter gamma-aminobutyric acid (GABA)[11]. Both are useful in neuropathic pain treatment at the oral dose of 300 mg of gabapentin and 150 mg of pregabalin[21]. They have good feedback for treatment of postoperative neuropathic pain when started early in the preoperative period as preemptive analgesia[21]. The side effects of prolonged use of pregabalin and gabapentin are excessive sedation, dizziness, and visual disturbances[21].

Opioid Free Anesthesia Protocol

According to studies in clinical practice, the modified versions of OFA technique by Mulier are mostly used[2]. The OFA protocol consists of preoperative administration of pregabalin or gabapentin and midazolam as premedication at least 1 hour before surgery on the ward[2,5]. Induction of OFA is usually started with anesthetic mixture of dexmedetomidine 10 to 20 minutes before intubation[2,5,7]. However, for accomplishment of adequate sympatholysis, analgesia and anesthesia co-induction with low doses of ketamine and lidocaine infusion 10 minutes before intubation is also recommended[2,5,7]. Since intubation is one of the most noxious stimuli, it is performed with additional bolus doses of intravenous anesthetic propofol and muscle relaxant in a dosage according to ideal body weight[2]. Maintenance of OFA is performed with the same mixture of opioid free anesthetics (dexmedetomidine, ketamine, lidocaine) and low doses of inhalation anesthetics with the goal of achieving minimum alveolar concentration of 0.5-1 vol.% and intraoperative hypnosis without recalling consequences according to bispectral index monitoring[2,7]. Unless this opioid free anesthetic mixture is not adequate for achieving satisfactory analgesia and anesthesia, magnesium infusion can be added as further co-analgesic[2,5,7]. If a surgery which requires patient neuromuscular blockade is performed (such as laparoscopic abdominal or gynecologic or bariatric surgery), it is recommended, according to Mulier OFA protocol, to maintain deep muscle paralysis with muscle relaxant infusion according to Train of Four monitoring to the end of surgery and appropriately reverse it at skin suture[2,4]. Opioid free anesthetics are usually discontinued 20 minutes before emergence[2,5,7]. Antiemetics are administered, together with dexamethasone bolus dose of 8 mg as adjunctive analgesic[2,7]. In addition, intravenous analgesia with paracetamol or NSAIDs is started, and local anesthetic infiltration at the surgical site is advisable[2]. Additional rescue analgesia with metamizole is provided according to patient hemodynamic stability and visual analog scale after emergence from anesthesia[2].

Discussion

We are stepping in the new era of anesthesia where we have to enhance patient postoperative recovery not only by better surgical technique but also by minimizing postoperative and postanesthetic side effects. Studies have shown that opioid based anesthesia has many side effects such as obstructive breathing, muscle rigidity, respiratory depression, dizziness, sedation, pruritus, shivering, urine retention, opioid induced bowel dysfunction including constipation, ileus, abdominal pain, and in the end, if unrecognized, the serious state of abdominal compartment syndrome, headache, nausea and vomiting, gastroesophageal reflux disease, narcotic bowel syndrome, opioid induced hyperalgesia, and opioid induced tolerance[2]. OFA is a way to rationalize and minimize the perioperative use of opioids. OFA

can also be a successful technique owing to better analgesia without or with less opioids, absence of PONV, anti-inflammatory activity, no rebound pain or hyperalgesia, suppressing the neuropathic pain component in the perioperative period, and stable perioperative hemodynamics with less stress and cortisol level elevation[5,22-25]. There are studies which show the benefits of OFA in plastic, ambulatory, gynecologic, and laparoscopic surgery[26-28]. Further studies are necessary for OFA in oncologic surgery[29]. However, so far, the main indication for OFA is bariatric surgery, obese patients, and patients with OSAS[2]. According to studies, acetaminophen, NSAIDs and cyclooxygenase 2 inhibitors bring 24%-31.6% of the opioid sparing effect and significant 30% reduction of opioid related adverse events[30]. Utility of nonopioid analgesics such as alpha 2 agonist, low dose ketamine, gabapentinoids, magnesium, dexamethasone contributes 20%-50% to opioid sparing[30-32]. In OFA, we use standard monitoring of patient vital signs as a mandatory method according to good clinical practice, such as pulse oximeter, electrocardiogram, blood pressure monitoring, temperature probe, oxygen analyzer, and carbon dioxide analyzer with respiratory parameters on the anesthesia machine, bispectral index monitoring for adequate hypnosis and Train of Four monitoring for adequate muscle blockade. The issue is intraoperative pain validation. Since pain is the fifth vital sign, there is no reliable device yet which can appropriately measure intraoperative analgesia and anti-nociception under surgical default besides the already mentioned circulatory variables such as blood pressure and heart rate. However, progress has been made on the market. There is a new smart noninvasive anesthesia monitoring Conox which acts as bispectral index monitoring[33]. It calculates two parameters from the patient's electroencephalogram. One is qCON index which correlates to the patient's level of consciousness[33]. Another is qNOX index which shows the patient's response to noxious stimuli[33].

Conclusion

To conclude, OFA is a technique which satisfactorily controls postoperative pain as the fifth vital sign. Studies have shown that, if used according to indications and contraindications, it maintains the same intraoperative condition as multimodal balanced opioid anesthesia, has postoperative opioid sparing effect, shorter duration in the post-anesthesia care unit and shorter hospital stay, PONV, and greater patient satisfaction[5].

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Sažetak

ANESTEZIJA BEZ PRIMJENE OPIOIDA U KLINIČKOJ PRAKSI – PREGLEDNI RAD

S. Sakan, Ž. Turudić, S. Peremin, A. Šribar, N. Sojčić, M. Čučković, D. Vergles i *J. Peršec*

Primjena protokola ERAS (*enhanced recovery after surgery*) u svakodnevnoj anesteziološkoj i kirurškoj praksi omogućava brži oporavak bolesnika nakon operacije uz minimalne poslijeoperacijske komplikacije. Prema dosadašnjim istraživanjima opća anestezija bez primjene opioida trebala bi biti dio protokola ERAS u svakodnevnoj kliničkoj praksi u skladu s primjenom prema unaprijed određenim indikacijama s obzirom na vrstu operacije i status bolesnika. Opća anestezija bez opioida je multimodalna uravnotežena tehnika koja se temelji na konceptu da se opioidni lijekovi ne primjenjuju prijeoperacijski i intraoperacijski sve dok se bolesnik ne probudi iz anestezije. Iako su novija istraživanja pokazala prednosti anestezije bez opioida u odnosu na opću multimodalnu uravnoteženu anesteziju s primjenom opioida, daljnja istraživanja su potrebna.

Ključne riječi: *Akutna bol; Multimodalna anestezija; Anestezija bez primjene opioida; Perioperacijsko razdoblje*