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Perioperative pain management of orthopaedic patients based on new guidelines and literature review

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Abstract:

The pain management is an important issue of orthopedics and traumatology. The choice of therapy should be based on proper assessment of pain, monitoring and appropriate selection of analgesics. The necessary knowledge about the pharmacokinetic and pharmacodynamic profile of the drugs allows to maximize the benefits and minimize the risks associated with the use of painkillers and The proper pain management affects the time between surgical intervention and rehabilitation. In spite of new analgesics and broadening knowledge about the mechanisms of pain, the results of treatment are unsatisfactory. Growing addiction to opioids is a major concern. A multimodal approach to pain management can provide better pain control and reduced opioid consumption. The purpose of this article was to review of the latest literature and recommendation to provide a summary of effective perioperative analgesic methods.

Keywords: trauma, management of pain, orthopedic surgery

Introduction and purpose

A pain is unpleasant sensory and emotional experience associated with both - actual or potentially threatening injury of the body or described in terms of such injury [1]. It may result from irritation of pain receptors (nociceptors) or reduction of their excitability threshold (receptor pain). Moreover, the pain can develop in case of damage to the structure of the nervous system (non-receptor neuropathic pain) or may appear without accompanying tissue damage (psychogenic non-receptor pain) [2]. The patomechanism of pain is mediated by neurotransmitters and excitatory amino acids that release the supplying neurons to process and modulate pain. The impulses can be transmitted by three types of nerve fibers with differentiated velocity. A-delta type fibers are responsible for ‚fast pain'. The pain transmitted through these fibers is well-located, sudden and stops after the end of stimuli. It should be underlined that the fibers do not possess the opioid receptors which explains why opioids should not be the only form of treatment for this type of the pain. Yet, it may be blocked by application of local anesthetics. Type C non-myelin fibers respond to a variety of stimuli; mechanical, chemical and thermal. Chemical stimuli includes inflammatory mediators such as: hydrogen ions, potassium ions, serotonin, histamine, prostaglandins, thromboxane, leukotrienes, cytokines and tissue kallikreins. These last ones are proteolytic enzymes that are activated in damaged tissues. They act on tissue proteins - kininogens by detaching active peptides-kinins (e.g. bradykinin) from them. These active forms depolarize naked nerve endings and trigger inward nerves of pain impulses. Kinins not only depolarize naked nerve endings, but also dilate blood vessels. The resulting inflammatory process activates the opioid receptors accumulated at the nerve endings and after a few days their number increases significantly. C fibers are responsible for rapid, non-localized pain that responds well to opioids [3]. Nociceptive activity of spinal cord is conducted to higher centers in the brain, where pain is modulated byendogenous opioids, noradrenaline, and 5-hydroxytryptamine (serotonin). These modulating substances are capable of enhancing or inhibiting pain.

Knowledge of patomechanism of pain development enabled the introduction of multimodal analgesia. It is based on the combining different groups of drugs and interaction at many levels of the formation and processing of the pain stimulus. Pain management is an important issue in the field of orthopedics and traumatology and is considered as one of the most important clinical standards. The choice of therapy should be based on a proper assessment of monitoring and selection of analgesics. The knowledge of pharmacokinetics and activity of individual drugs helps to avoid pain episodes in patients and thus affects the time between surgical intervention

and rehabilitation. Adequate pain control is important step towards therapeutic success and indirectly into the time and costs of hospitalization and patient satisfaction [18]. In spite introduction of new generations of analgesics and broadening the knowledge considering the mechanisms of pain development, the results are still unsatisfactory. Inadequate pain control negatively affects the healing process of wounds and also increases the risk of immunosuppression or infections. Ineffective pain inhibition prevents early mobilization of the patient that increases the risk of pulmonary embolism and thrombosis[4]. Additionally, it elongates the time of patients hospitalization that decreases the level of both - the satisfaction of the patient and the reputation of treatment unit deteriorates.

Description of the state of knowledge

It is recommended to avoid subcutaneous or intramuscular analgesic administration in both preoperative and postoperative periods, as hypothermia and hypovolemia and thus hypoperfusion may affect drug distribution. The intravenous administration should be used especially after major surgeries. In-hospital conditions allow the use of differentiated analgesic techniques and medications. The decision concerning the method of analgesia in this group of patient is complicated and depends of variated factors such as: type and extent of injuries sustained, cardiovascular and respiratory fitness, the presence of comorbidities, the state of the coagulation system, known drug allergies, current nutritional status and others [5]. The combination of drugs from different groups enables to minimize the dose with unchanged analgesic strength. Combining drugs is particularly recommended for extensive operations and procedures with a high risk of chronic pain. Regarding the period following operation, the treatment should be applied to enable reliable diagnostic procedures. It is worth emphasizing the role of short-acting opioids, e.g. remifentanl, while keeping in mind that they can cause drowsiness and thus cause difficulties in assessing patients after craniocerebral trauma.

Opioids

These drugs affect opioid receptors and are used in therapy of moderate and severe pain. They differ in their potency, affinity for different receptorsand side effects. The knowledge of these differences is substantial to fully exploit the potential of these drugs. It should be underlined that apart from analgesic effect, opioids act on different structures such as respiratory, digestive and cardiovascular systems. Additionally, opioids modulate the mood and behavior as well as immunological system increasing the risk of infections [6]. The most common side effects include constipation, itching, nausea, vomiting, sedation, difficulty breathing and respiratory

depression [7]. The use of multimodal analgesia enables to reduce the dose of opioids by combining them with co-analgesics (ketamine, lidocaine, gabapentin) or other non-opioid drugs. Opioids should be used intravenously for perioperative therapy. The dose should be determined based on titration - the administration of small doses of the drug in short intervals, until satisfactory pain control is achieved and this dose is continued by continuous intravenous infusion. In practice, morphine is implemented in dose of 1-2 mg in 3-5 minutes intervals. Knowing the half-life of morphine, which is about 3-4 hours, the infusion rate may be calculated. For a saturating dose of 12 mg it will be 2 mg/h [7]. The PCA method - patient-controlled analgesia (bolus 0.5-2.5 mg and refraction time5-10 minutes) can also be implemented. It is also worth remembering the 1: 3 rule describing the ratio of intravenous dose to subsequent oral dose. In the postoperative period, when possible, opioid administration should be provided via enteral rout because the advantage of intravenous supply over oral has not been proven. Normally, the oral dose of morphine is estimated to 5-10 mg every 4 hours (short-acting preparations) or 10-20 mg every 12 hours (controlled-release preparations).If we know the dose of morphine that brings satisfactory pain control, it can be effectively replaced with another opioid drug using the equivalent dose converter. Such attempt allows to adjust the pharmacological profile and reduce the number of side effects. In recent years, there have been reports of adverse effects of opioids that cause immunosuppression, worse wound healing, increased risk of perioperative complications, and the phenomenon of opioid paradox. The phenomenon of respiratory depression is especially dangerous in case of patients suffering from chronic obstructive pulmonary disease and the ones applying simultaneously the drugs that depresses the nervous system such as benzodiazepines or antidepressants. That is why, opioid free anesthesia/analgesia (OFA) is becoming more popular.

In first days after procedure, short-acting opioids in the bolus should be introduced. Routine intravenous opioid infusion is not recommended. Moreover, the proper monitoring of saturation level, number of breaths, signs of hypoventilation and depth of sedation should be sustained. Due to the growing popularity of opioid use, especially among surgical patients, there is a high risk of eradication of opioid tolerance. The opioid tolerance is defined as taking orally more than 60 mg of morphine (or morphine equivalents) per day for period of time of 1 week [8]. The opioid tolerance creates many challenges to pain management, including balancing out pain control with drug side effects. The patients that tolerate opioids are in need of higher doses of the drugs in order to achieve proper pain control. It increases the risk of potential toxicity of

opioids including respiratory depression. However, there is still a lack of relevant literature on perioperative pain management in this group of patients.

The United States is facing an opioid crisis because opioid prescription has quadrupled since 1999 and increased in parallel with the number of overdoses of the most commonly prescribed opioids [9]. Even the opioids that are prescribed for operations with low pain risk, they still increase the risk of opioid dependence for short period of time. More than 60% of people receiving continuous opioid treatment for 90 days will develop addiction symptoms in future years [10]. The risk factors for post-opioid dependence among patients who have not previously used opioids include: male sex, age over 50, preoperative use of benzodiazepines, preoperative use of antidepressants, history of depression, history of alcohol abuse and history of drug abuse. Finding ways to minimize the risk of addiction is particularly important regarding current literature. As an alternative to opioid use, it offers multimodal analgesia consisting of 2 or more drugs. The components of multimodal analgesia often include gabapentenoids, acetaminophen, ketamine, NSAIDs and local anesthesia. In a meta-analysis of 52 randomized studies involving 4,893 adults, acetaminophen, NSAIDs or selective COX-2 inhibitors significantly reduced 24-hour morphine intake after surgery [11]. The concept of multimodal analgesia is no different from current multi-drug treatment of various other conditions, including hypertension, diabetes or asthma. For example, during treatment of asthma, prescribing exclusively beta-mimetic drugs for obturation control without application of corticosteroids to combat inflammation would be inappropriate. The implementation of medicaments with different mechanism of action may provide important clinical benefits and increase analgesic efficacy.

Non-opioid anelgetics

Non-opioid anelgetics are recommended as the first-line treatment in case of acute and post-operative pain because they reach peak concentrations most quickly after intravenous administration that correlates with peak of their analgesic action. The contradictions of these drugs application would be both - renal and hepatic failure. Pharmacodynamically important is the fact of having ceiling doses beyond which no increase in analgesic effect is observed, but an increase in adverse effects.

Paracetamol is an effective drug that shows the an additive effect in combination with other drugs. For example, combination of paracetamol with ibuprofen creates the additive effect and dexketoprofen applied tramadol and paracetamol show hyper additive effect. It can also be used

effectively in advance analgesia. According to the latest reports, paracetamol works at all stages of pain conduction, however, it has no anti-inflammatory effect, therefore its use is justified in the case of somatic nociceptive pain.

Metamizol due to its additional spasmolytic effect is a valuable drug for visceral nociceptive pain. Moreover it has an additive analgesic effect in combination with paracetamol and other NSAIDs.

NSAIDs

Nonsteroidal analgesics (NSAIDs) work by inhibiting prostaglandin cyclooxygenase and possess anti-inflammatory, analgesic and antipyretic effects. Additionally, NSAIDs influence other processes that take part in the development of nociceptive inflammatory pain. In everyday clinical practice, it should be remembered not to use more than one drug from this group because they do not show synergistic effects. What is more, the combination of two NSAIDs can increase the toxic effect of those drugs. The main side effects include the upper gastrointestinal tract, the cardiovascular system and the kidneys (especially for patients taking furosemide).

During postoperative period, the application of NSAIDs in analgesic treatment has shown reduced bone healing abilityin animal studies yet no statistical significance was found in human studies [12,23].

Selective COX-2 receptor inhibitors (celecoxib, etoricoxib)

An important issue regarding pain management in field of orthopedics and traumatology is the implementation of selective COX-2 receptor inhibitors. Available studies describe the beneficial effects of those drugs in pain control as well as the minimized need for introduction of the opioids in case of orthopedic patients [13]. Moreover, celecoxib has been shown to prevent the formation of non-skeletal ossification and to reduce the risk of gastrointestinal adverse effects compared to non-selective NSAIDs [14].

The adjuvants in analgesic treatment

Considering the subject of analgesia, it is worth mentioning the use of adjuvants, the substances that do not have an analgesic effect themselves but in combination with other drugs, they reduce

their doses. Intravenous lidocaine in the preoperative and intraoperative period has been shown to reduce opioid doses in the postoperative period. In addition, it reduces the incidence of postoperative nausea, vomiting and accelerates the return of intestinal motility. This use of lidocaine is most effective for major abdominal surgery [15]. On the other hand, there are scientific publications concluding that lidocaine may be used in spinal surgery, but the amount of scientific data is limited. Lidocaine is administered as a 1.5 mg/kg bolus as a loading dose followed by an infusion of 1-3 mg/kg h. Dosage should be calculated based on the body weight of the patient. Lidocaine infusion is contraindicated in operations involving regional anesthesia - especially in the case of plexus blockade where local anesthetic is given in high doses. Magnesium sulfate is another known co-analgesic administered in a bolus dose of 50 mg/kg followed by an infusion of 10-15 mg/kg/h[16].This substance reduces the daily amount of opioids administered also in orthopedic surgery. Magnesium ions may contribute to bradycardia and delay of conductivity. Nevertheless, the application of magnesium sulfate is considered as safe and effective. Other analgesics are: gabapentinoids, clonidine, dexmedetomidine, and corticosteroids.

Administration of local anesthetics

As part of multimodal analgesia, injection of the surgical site with a solution of bupivacaine or lidocaine or mixtures with the addition of NSAIDs is used. According to current knowledge, such a procedure in the case of total knee prosthesis [17] or spine surgery [18] reduces operating pain and opioid consumption without showing the adverse effects. The introduction of infusion of locally anesthetic drugs directly to the wound proves to be an effective and safe method. Main concerns relate to the placement site and risk of infection associated with the inserted catheter. Therefore, further studies with a larger patient group and longer follow-up are recommended[19]. According to available meta-analyzes, LIA is effective in the treatment of acute pain after TKA. Intraoperative periarticular but not intraarticular injection may be helpful in controlling pain for up to 24 hours. The use of postoperative delivery catheter is still ambiguous [20].

The way of choosing medicines

In 1986, the World Health Organization proposed the use of an analgesic ladder, which optimally describes the process of introducing subsequent drugs depending on the severity of pain. At the same time, she emphasized the rightness of using co-analgesics. The analgesic ladder has been used successfully to this day, especially for patients undergoing cancer. One of

the key elements of effective post-operative pain relief is measuring its intensity. Pain intensity should be systematically assessed both at rest and in dynamic conditions (dressing change, coughing).It should be emphasized that according to the difficulty of controlling the patient's pain, they do not have to be directly proportional to the extent of the procedure.

In Gerbershagen et al., Which compared pain intensity on the first day of surgery, it was proved that small and medium procedures, including some laparoscopic procedures, resulted in unexpectedly high levels of postoperative pain. This was due to incorrect assessment of pain intensity in patients by medical staff. [21] In practice, the most recommended in older children and adult patients is the numerical rating scale (NRS). Each time the result of the measurement should be recorded in the patient's medical records. For practical purposes, the following pain ranges are assumed using the NRS or visual analogue scale (VAS):

- mild pain: 1–4 on the NRS / VAS scale,
- moderate pain: 5-6 on the NRS / VAS scale,
- severe pain: 7 and above on the NRS / VAS scale.

In the case of mild pain (1-4 on the NRS or VAS scale), one of the non-opioid analgesics, i.e. paracetamol, metamizole and / or one of the nonsteroidal anti-inflammatory drugs (NSAIDs) should be used. In the case of moderate pain (5-6 on the NRS or VAS scale), a combination of non-opioid analgesics, i.e. paracetamol, metamizole and one NSAID with a weak opioid, tramadol, which may be administered intravenously or orally, should be used. In the event of nausea and / or vomiting that may occur after administration of tramadol, do not use metoclopramide or ondansetron, as these drugs may reduce the analgesic efficacy of tramadol [10; 22]. I suggest combining regional blockades with systemic treatment as part of multimodal therapy. However, remember to avoid opioids when they are not necessary because of side effects.

Treatment should be tailored to the patient's subjective feelings and not to the physician's assumptions about the extent of the surgery. A’Court et al. They compared the severity of pain after Hip hemiarthroplasty and dynamic hip screw (DHS) fixation. Patients undergoing dynamic hip screw (DHS) fixation required twice higher opioid doses than patients after Hip hemiarthroplasty. [24]

Polish guidelines for the management of postoperative pain from 2018 give examples of the use of painkillers in three specific orthopedic operations. For arthroscopy, paracetamol and / or NSAIDs are recommended. Metamizole and tramadol can also be used. All drugs should be administered orally as much as possible, and when pain disappears, the number of drugs should be reduced without dose reduction. After hip replacement, it is recommended to continue epidural anesthesia if it was used during surgery or using coxib (clelecoxib) p.o. or a combination of NSAIDs (i.v. or p.o) with paracetamol (p.o. or i.v.). In the event of severe pain, opioids should be added to the medication used. In the case of knee prosthesis, it is recommended to continue the peripheral blockade (continuous infusion or PCA) or NSAIDs (coxibs), and in the case of severe pain, to combine opioids with paracetamol [16].

Phenomenon of persistent pain

Phenomenon of persistent postoperative pain (occurring more than 3 months after surgery) may occur in predisposed persons: physically disabled and obese, and in the case of particularly difficult technically and extensive procedures. For prevention, regional analgesia, preventive analgesia or advance analgesia can be used. Advance analgesia minimizes central nervous system blockage before the increase of affective nociceptive stimulation occurring during surgery, which in turn leads to a reduction in the development of peripheral and central sensitization. In order to induce the effect of "analgesia in advance", it is recommended to use different groups of drugs and methods, such as conduction anesthesia techniques, gabapentinoids (gabapentin, pregabalin), opioids, nonsteroidal anti-inflammatory drugs, paracetamol, metamizole, NMDA receptor antagonists (ketamine, dextromethorphan), agonists alpha-2 receptor (clonidine, dexmedetomidine), tricyclic antidepressants (e.g. doxepin), or cytokine activation modulators (e.g. lidocaine iv) [24]. Celekokspb at a dose of 400 mg given one hour before surgery has been proven to contribute to pain relief after knee arthroscopy surgery [13,14]. It is worth remembering that neuropathic pain may also appear in patients after surgery. This is a burning / burning pain that usually occurs a few days or weeks after the injury. It is a consequence of damage to the structures of the central or peripheral nervous system as a result of trauma, and the therapeutic management is different than in the case of pain syndromes accompanying injuries of somatic or visceral structures.

Summary

There are many different pain regimens available for orthopedic patients that have demonstrated clinical efficacy. According to the latest literature, the multimodal approach has

the advantage over single opioid therapy, using many different groups of drugs acting at different levels of pain conduction. It helps reduce opioid consumption and thus the risk of addiction. Pain management should be based on the patient's subjective feelings using available scales.

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