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POSTOPERATIVE AND CANCER PAIN NEED PROPER ANALGESIA

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ABSTRACT:

The authors surveyed the clinical data and reviewed the literature on the management of post-operative and cancer pain. The conclusion was made that pain management during post-operative period or in status of advanced cancer necessitates effective pharmacotherapy with non-opioid and opioid analgesics. Data for pharmacokinetics and pharmacodynamics of widely used analgesic drugs are listed. The authors provide practical guidelines for the management of post-operative and cancer pain in clinical wards as well as in outpatients departments.

Key words: post-operative pain, cancer pain, pain management, opioids, non-opioid analgesics, pharmacokinetics, pharmacodynamics,

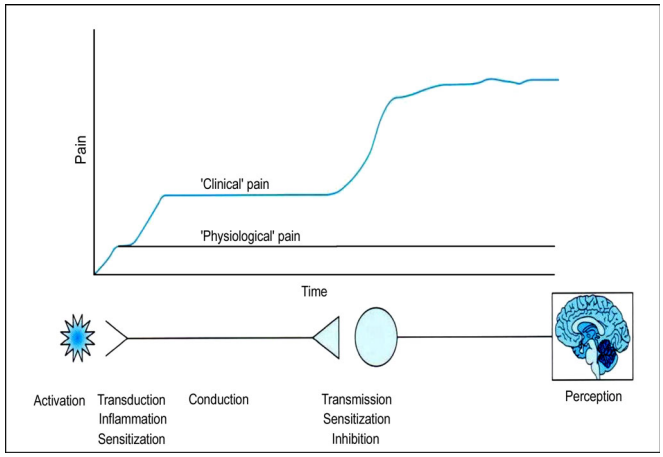
Despite the remarkable progress in clarifying the mechanisms and treatment of postoperative pain, it is a serious problem in the clinical settings. A significant number of patients still experience moderate to severe pain following different surgical procedures [1]. The necessity to implement an integrated approach for treatment of postoperative pain, combining organizational, pharmacological, psychological and instrumental approaches is evident.

Pathophysiological mechanisms

Postoperative pain is a severe pain with multiple pathogenesis and complex clinical symptoms, involving unpleasant sensory, emotional and psychological components arised by surgical procedures triggering autonomous, hormonal- metabolic, psychological and behavioral reactions in the patients. It is well known that the activation of nociceptive mechanisms in undamaged tissues usually cause permanent and adequate (to the allogenic irritation) nociceptive reaction. The peripheral nociceptive terminals transform chemical, thermal or mechanical stimuli into electrical activity, transmitted to the posterior horns of spinal cord and the subcortical nuclei and cortical centers of pain. The experienced in that situation pain can be provisionally called physiological, since it carries information about the potential damage to the organism [2]. In majority of the primary sensory neurons, the principle neurotransmitter is glutamate and during their activation as neuromodulators, a number of other substances are released. Specialized endogenous defense mechanisms against the excessive pain exists in the body and build a descending antinociceptive system. Tissue damage activates a number of neurohumoral cascades, inducing reversible changes in the excitability of peripheral and central nociceptive pathways (modulation or sensitization) causing thus in many patients, severe pain and increased pain sensitivity during the postoperative period. Pharmacological treatment, aiming to achieve an effective postoperative analgesia, is directed towards suppressing exactly these processes.

The excessive depolarization in central nociceptive pathways may induce destructive changes and death of inhibitory interneurons, manifested as disinhibition. The formation of new synaptic contacts between the low-threshold mechanoreceptors and the neurons in the posterior horn of the spinal cord (synaptic reorganization) are irreversible and resistant to therapy with analgesic drugs. The consequences thus are irreversible changes in the peripheral and central nociceptive pathways and transformation of the severe pain to a chronic one. A simplificated scheme of general nociceptive mechanisms is depicted on Fig. 1.

Fig. 1. Main cellular and integrative mechanisms of severe pain (modified by [3])



The processes of peripheral and central sensitization increase the incoming nociceptive impulsation, causing threshold lowering and increase in pain intensity.

Preclinical and clinical observations

The evaluation of postoperative pain must validate not only the intensity of pain at rest, but also the dynamic pain during one's normal activity and the effect of administered analgesic therapy on the perception. The quantification of pain intensity is performed by verbal or visual

scale. According to the former scale, the pain is graded as absent, weak, moderate and strong, and the analgesic effect is defined as zero, weak, moderate, good or complete. According to the latter method, the pain is measured with marked scale in centimeters, 10 cm in length, in which *zero* means no pain and 10 indicates the *strongest possible pain*. Some convincing clinical data indicates that concerning the intensity of postoperative pain, patient's objective evaluations by the verbal or the visual scale practically do not differ from each other. Comparative clinical studies describe that, when using analogue visual scale, patients rate the intensity of pain after orthopedic arthroplasty surgery at the 30 mm from the start of scale, they would most likely determine the pain as "moderate" in the four-grade analogue verbal scale [4]. Almost all surgical procedures are invariably accompanied by incision of the skin or mucous membranes - mechanically, thermally and/or chemically-induced tissue trauma, combined with prolonged stretching and retractation of superficial and visceral structures. It is generally accepted that the acute postoperative pain is a typical nociceptive one. Inflammatory, visceral and neuropathic components contribute to the complex pathogenesis of acute postoperative pain, as well as, potentially, the development of neuronal sensitization. In this aspect it is interesting to emphasize that experimental [5] and clinical [6] models of post-surgical pain established the existence of primary and secondary hyperalgesia. They are mediated by NMDA-receptor mechanisms [7] and central sensitization [8]. After surgical procedures, allodynia and hyperalgesia induced by reduced nociceptive threshold and/or compromised sensation of pain, are observed in areas around the skin incision [9]. As an useful recommendation the opinion could be considered, that the use of scales to rate the analgesic effect is more adequate approach in clinical practice, than the one using scales to rate the intensity of pain. Tissue damage during a surgical procedure, triggers series of endocrine, metabolic and inflammatory reactions, that on one hand contribute to pain sensation and on the other, contribute to the dysfunction of organs involved and results in complications, longer hospitalization and in extreme cases – to the unfavorable course of postoperative period. It should be taken into consideration, that the severity of postoperative pain clearly correlates with the severity of operative trauma. This is schematically presented on Tabl. 1.

Tabl. 1. Clinical reactions and effects induced by a surgical procedure.

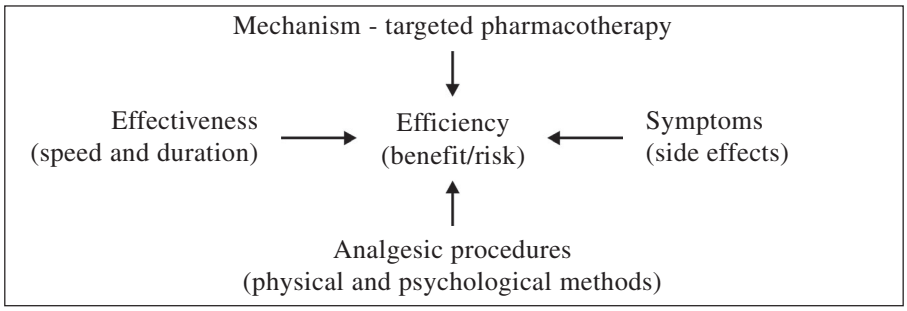
Local and systemic inflammatory reactions	**Neurogenic - mediated reactions**
• Proinflammatory cytokines IL-1, IL-6, TNF (+) • Antiinflammatory cytokines IL-10 (-) • Coagulation / fibrinolysis (+ / -) • Acute phase proteins (+ / -) • Other cascades (+ / -)	• Catabolic hormones Cortisone, catecholamines, glucagon (+) • Anabolic hormones Insulin, testosterone (-) • Autoimmune reactions (+) • Pain (+) • Sensory aferentation (-)
Clinical effects	**Clinical effects**
• Immunosuppression Infections metastases • Pulmonary complications • Thromboembolic processes • Hypothermia, fatigue • Ileus • Pain	• Catabolic processes Loss of muscle mass • Pulmonary complications • Cardiovascular complications • Sleep disorders • Ileus • Pain

IL - interleukin, TNF - tumor necrosis factor (+) increase (-) decrease

Mechanism - targeted diagnostic and therapeutic approaches

Sufficient number of clinical observations indicate, that significant discrepancy exist between the theoretically improved chances to relieve postoperative pain and the relatively low actual relief of postoperative pain that patients gain in real clinical settings [10]. The utilitarian approach in treating postoperative pain probably suggests one to be familiar with all the factors involved in pathogenesis of pain post surgical procedures. Such an approach is more adequate for chronic pain treatment, but doesn't help in achieving adequate postoperative analgesia. In contrast to the chronic pain, acute pain requires immediate treatment, so the application of mechanism - oriented approach is restricted. In this context, it is understandable why there is no mechanism - targeted diagnostic and therapeutic approaches about acute postoperative pain treatment options in specific clinical cases [11]. Nonetheless, the clinical experience indicates, that traditional analgesic medications have equal effect in different models of acute postoperative pain [12]. The empirical clinical experience on other hand indicates that efficient relief of postoperative pain can't be achieved with analgesic monotherapy only. Therefore, it is recommended to follow a more balanced approach towards the medication induced analgesia – specifically, a multimodal therapy with analgesics having various mechanisms of action [3]. We could suggest that a system able to provide optimal treatment of postoperative pain should be in accordance to the algorithm presented on Table. 2.

Table 2. Algorithm for the treatment of acute postoperative pain.



Pharmacological medications and antinociceptive procedures

Postoperative pain relief is an important factor for early and successful recovery post surgical intervention. It should be taken into consideration that the onset of potential complications such as postoperative stress and / or functional disorders in certain systems and organs could be influenced by the applied analgesic medications and procedures. Routine practice prescribes to start the treatment of acute postoperative pain with NSAIDs or coxibs. These agents, however, have only minor effect on postoperative stress, catabolic stress hormones and protein synthesis [13]. The trivial scheme for treatment of postoperative pain uses the application of paracetamol (per oral or i.v.) with or without opioid. A dose of 1.0 g paracetamol per os decreases the dose of post major surgery opioid analgesic more than two-fold. The classic NSAIDs have a slightly better analgesic effect, but more severe adverse reactions. Coxibs have similar analgesic profile and weaker gastrointestinal side effects. So as a rule of thumb, it may be assumed that paracetamol is the drug of choice in postoperative analgesia [3]. Opioid analgesics used in trivial schemes in low dose patient-controlled analgesia, have good effect on postoperative pain, but only minor effects on postoperative stress. Intraoperative opioid analgesia in higher doses has beneficial effect on post-operative stress. Needless to say, all approaches that could directly relieve the post-operative pain are the approaches of choice. In this context, neural blockade with local anesthetics is currently referred as a highly effective approach to relieve postoperative pain and stress. Some of the most frequently observed adverse effects after applying local anesthetic neural blockade are presented on Tab. 3.

Table 3. Adverse systemic effects after application of neuronal blockade with local anesthetics.

Pituitary gland	Adrenal glands	Metabolism	Immune system
β - Lipotropin (+)	Cortisol (+)	Hyperglycemia (+)	Lymphopenia (+)
ACTH (+)	Aldosterone (+)	Insulin (-)	C3a, C5a complement (-)
β- endorphin (+)	Renin (+)	Lipolysis (+)	NCC (-)
GH (+)	Adrenaline (+)	N_2 - balance (-)	
TSH (+)	Noradrenaline (+)	O_2 - consumption (+)	
LH (+)		Urea (+)	
FSH (-)		K^+ - excretion (+)	

FSH follicle stimulating hormone, GH growth hormone, LH luteinizing hormone, NCC natural killer cells, TSH thyroid stimulating hormone, (+) increase (-) decrease

Patient - controlled opioid analgesia is a routine method to relieve postoperative pain. In this approach, alongside relieving the acute pain, patient's mitigation and a reduction of the continuous medical supervision is achieved. By contrast, data from meta-analysis of 33 randomized control trials indicate that patient-controlled analgesia has no definite priority over the trivial intermittent opioid analgesia [14]. In everyday surgical practice, central blockade by local anesthetics remains one of the most preferred procedures for postoperative analgesia. Analysis of several randomized studies established that epidural or spinal analgesia with local anesthetics is very efficient, reducing the risk of pulmonary, vascular, renal and intestinal complications in major orthopedic surgery at the same time [15]. There is no convincing data about the advantage of continuous drip infusion over the interrupted parenteral application. In contrast, the combined epidural infusion of local anesthetic with an opioid has major advantage, with its pronounced analgesic effect and minor postoperative complications. In rare cases, combined epidural infusion of local anesthetic or opioid analgesic with clonidine or adrenaline is preferred. Schematic overview of the mechanisms, pathways and pharmacotherapy of postoperative pain is depicted on Table. 4.

Table 4. Mechanisms, processes and mechanism-targeted of treatment of acute postoperative pain

Mechanisms	Processes	Mechanism-acting analgesics/ procedures
Transduction	Transformation of algogen stimulus (surgical trauma) into nerve impulses.	NSAIDs, coxibs, steroids, topical opioids
Peripheral sensitization	Lowering of nociceptor threshold of pain (autosensitization) or hyperexcitability of membrane from sensitizing agents (heterosensitization).	
Translation	Propagation of impulses from sensory nerve to posterior horn of spinal cord .	Topical anesthetics (infiltration, blockade, epidural, spinal anesthesia), clonidine.
Transmission	Transmission of algogen signals from primary afferents to secondary nociceptive neurons in the spinal cord via neurotransmitters.	Opioids, adrenaline, a_2-agonists (clonidine), neostigmine.
Inhibition	Activation of segmental and descending inhibitory neurons in CNS.	
Central sensitization	Hyperactivity of wind up nociceptive neurons, facilitation and disinhibition.	Preliminary analgesia, NMDA antagonists (ketamine, dextromorfan, NSAIDs, coxibs, gabapentin).
Modification	Lasting or permanent changes in sensory neurons and central pathways by gene dysregulation, abnormal connections, cell death.	Enhanced protective preoperative analgesia.
Perception	Identification and interpretation of initial perception of pain in somatosensory cortex and other cerebral areas.	Opioids, tranquilizers, psychotropic medications.

CONCLUSION

Postoperative pain has multi-stage pathway, which could not be fully controlled at present. One should be borne in mind that if the patient's subjective rating of post-operative pain is over 3 on the 10-point visual scale effective treatment is necessary. A pragmatic approach seems to be the application of impacts of peripheral level, i.e. on the surgical wound and adjacent areas. In this context, elaboration of long-acting and slow-release (microbeads) local anesthetics is needed. Quite useful could be to develop pharmaceutical forms of opioid analgesics for nasal, sublingual or subcutaneous administration. In the near future, a preoperative assessment of patient's nociceptive predisposition should become a standard column in the pre-op checklist.

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