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Chapter

Introductory Chapter: The Rationale for a Multimodal Approach to Pain Treatment

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1. Common issues in acute and chronic pain management

The symptom pain is a perception affected by complex interconnections of biological, psychological, and social factors. Analgesic monotherapy can often provide pain relief in clinical conditions featuring non-severe pain. In other circumstances, such as those characterized by intractable cancer pain, or concerning acute/chronic non-cancer neuropathic pain, the intensity and quality of the pain require individualized multidrug approaches, with different analgesics and adjuvants used in combination according to clinical practice guidelines published by international and regional professional associations [1]. Moreover, because pharmacological strategies may not be able to successfully treat all patients with acute or chronic pain, nonpharmacological strategies should be included in the analgesic program, supporting and strengthening drug therapy [2]. Again, especially, chronic pain represents a dynamic experience, profoundly changeable in a spatial-temporal manner; thus, standardized and fixed protocols are not universally applicable for pain therapy. From these premises, the individualized, dynamic, and multicomponent pathway is summarized by the concept of the multimodal approach to pain management and represents a real revolution in this field of medicine. This optimization strategy can allow managing the pain by treating this symptom in its variegated clinical expressions through multiple interventions. According to the concept of multimodal therapy, the objective of pain relief is possible by targeting different sites of the nociceptive pathway [3] and by managing the galaxy of pain-related conditions through pharmacologic and nonpharmacologic modalities [4]. However, several considerations should be addressed in order to better understand its rational application for both acute (e.g., postoperative) and chronic pain management.

1.1 The unmet need of postoperative pain relief

According to the Lancet's data, more than 230 million people undergo surgery each year worldwide and this huge number tends to increase year over year [5]. Postoperative pain is a typical example of acute pain and, probably, it represents the classic example of unmet need in surgery as up to 80% of postsurgical patients experience pain which in 10–20% of cases is described as severe [6]. This topic is of paramount importance, as inadequately controlled pain impairs quality of life (QoL) and functional recovery, increases the risk of postsurgical complications, and lengthens the time of hospitalization. Increased morbidity and prolonged opioid use during and after hospitalization are serious problems which call for effective preventive interventions. Furthermore, treating chronic pain induced by ineffective

acute pain management increases the cost of care, enormously [7]. From these data, it is clear that the commonly used strategies to address postoperative pain are very often inadequate.

1.2 The issue of pain chronitization

Undertreated acute postoperative pain is the main cause determining the development of postsurgical chronic pain (PSCP), which is difficult to treat and often invalidating in form. The pain chronitization is the final stage of a complex pathogenetic cascade. Summarizing, these mechanisms involve the activation of peripheral and central sensitization pathways. Data from a wide number of preclinical investigations demonstrated that activation and sensitization of peripheral nociceptors, spinal dorsal horn neurons, and central nervous system (CNS) brain areas may occur [8]. The role of specific peripheral mechanisms contributing to pain after surgical incision and manipulation has been investigated as well. The literature on the topic encompasses an incredible number of studies on nociceptors, molecular mechanisms, fiber sensitization processes, inflammatory cytokines, and so on [9–13]. While according to a classical point of view, the CNS involvement is strictly related to the mechanisms of chronic pain; however, it may result in difficulty to identify the borderline between acute and chronic pain. There are many good reasons to believe that many gaps such as the role of the environment (i.e., epigenetic) and genetics are not still well explained. Again, no clear criteria for diagnosing central sensitization have been recognized. The chronicity of pain is the effect of changes in pain processing through transcription and transduction processes. Preclinical studies suggested that alterations in the mRNA expression occur within the first 42–48 hours after surgery [14]. These sensitization processes seem to be quite rapid, at least in the experimental field. Thus, postoperative pain is a convoluted process engaging both the peripheral nervous system (PNS) and the CNS and, in turn, the exact distinction between acute and chronic postoperative pain is not always easy to establish.

1.3 Toward an early and combined strategy

Rather than dissecting the precise pathophysiology of acute and chronic pain, our knowledge on the matter must be translated in the most effective way to limit acute pain and to prevent mechanisms of sensitization. For these aims, all our "analgesic arsenal" must be defused as soon as possible, and before that surgery may trigger the first fuse. For instance, it has been demonstrated that tailored preoperative educational programs reduced postoperative opioid requirement and shortened the length of stay [15]. Furthermore, several self-management programs focused on patient's education and training may reduce risk factors (e.g., lifestyle-related), enhance protective factors, and, finally, prevent pain chronitization [16]. As a consequence, individualized programs for perioperative pain management can be performed by acting simultaneously on different targets or implementing different strategies according to the timing.

1.4 The opioid crisis

Ineffective management of perioperative pain and poorly controlled postoperative pain may induce development of PSCP, increased opioid prescription and use, until opioid addiction. Because the opioids epidemic in the United States and Canada is a dramatic phenomenon which has been responsible for up to 70,000 drug overdose deaths, in 2017 [17], the time has come to look at more effective

solutions and less harmful approaches capable of inducing optimal pain relief combined with lessening opioid use, opioid prescriptions, and reduced opioid-related complications. Controlled investigations and evidence-based analysis demonstrated that multimodal approaches to postoperative pain improved analgesia and lowered opioid consumption is several clinical settings such as those underwent orthopedic [18] or colorectal surgery [19].

1.5 Chronic pain

These problems, linked to a lack of efficacy and to a criticality due to the use of opioids, do not only concern the postoperative pain chapter but also involve the management of chronic pain in its two sides of the coin, chronic cancer pain and chronic non-cancer pain. To understand the numerical terms of the matter, chronic pain is among the most common reasons for seeking medical care because it is reported by up 50% of patients seen in primary care [20]. Of note, chronic pain with neuropathic features, which often represents a hard task for clinicians, seems to be more common in the general population than earlier reported [21]. Because in cancer patients, pain has a multifactorial etiology and is quite a dynamic process, its management should be conducted through a careful combination of pharmacological agents with nonpharmacological strategies. This dynamical approach should be based on pain intensity and the complexity of symptoms, pain pathophysiology, and presence of comorbidities.

2. Features of the multimodal approaches to pain management

The concept of "multimodal" analgesia was introduced by Kehlet and Dahl, in 1993 [22]. This approach is based on the use of two or more distinct methods or drugs to treat pain rather than using opioids, or other strategies, alone. The rationale is that by combining medications and techniques with different mechanisms and sites of action, better pain relief can be achieved, with reduced side effects [23]. Different combinations of analgesic medications, adjuvants, and procedures can act on different sites and pathways in an additive or synergistic fashion. Clinicians may choose among a wide range of options included in several categories: pharmacologic, physical medicine, education and behavioral approaches, interventional, and surgical modalities. In the surgical setting, anesthesiologists may combine regional anesthetics, and/or nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX2) inhibitors, NMDA-receptor antagonists, and antiepileptic, and antidepressant medications with or without conventional opioids. On the other hand, chronic cancer and non-cancer pain chronic cancer treatment often requires the involvement of a multidisciplinary team which combines resources based on the patient's needs, obtaining an individually tailored program.

2.1 Surgical settings

Multimodal approaches to pain management can be included among more complex systematic processes adopted for managing the whole perioperative course. The Enhanced Recovery After Surgery (ERAS) pathway, for instance, is a multidisciplinary model of care born with the aim of guaranteeing optimal recovery and an early and safe return to daily activities after surgery. The pathway is a patient-tailored process provided by a team of surgeons, anesthesiologists, nurses, nutritionists, and physical therapists. In this scenario, the perioperative pain management is a keystone of the whole pathway [24]. Indeed, reduced need for opioids

through regional anesthetic block used in addition to general anesthesia during surgery, or other minimally invasive approaches, may be effective for both pain relief and enhanced recovery target [25]. Apart from the ERAS strategy, another recent approach to perioperative pain management is the so-called opioid-free anesthesia (OFA) [26]. This term refers to a fascinating option for anesthesia administration that maximizes the patient's comfort (including pain relief) while eliminating the unwanted side effects of opioids. Through this model, no intraoperative systemic, neuraxial, or intracavitary opioid is administered during the anesthetic course. The rationale of the OFA model is the avoidance of the opioid-induced hyperalgesia phenomenon, a paradoxical effect in which opioid therapy enhances or aggravates preexisting pain [27], the reduced occurrence of postoperative delirium, and postoperative cognitive dysfunction in elderly [28, 29] and in high-risk patients [30]. Furthermore, the OFA technique seems to be appropriate for minimizing respiratory depression in patients that have impaired respiratory function (e.g., due to sleep apnea, or obesity), for reducing postoperative nausea and vomiting, and for treating patients who have chronic pain conditions, or are on chronic opioid therapy, or opioid addiction [31, 32]. Although the effect of opioids on cancer recurrence or progression remains an open issue [33], the OFA approach can be considered as a protective strategy against cancer progression [34]. In the surgical setting, it is possible to obtain a multimodal strategy without completely avoiding opioids. Low-dose opioids can be combined with one or more additional pain management methods (e.g., peripheral nerve blocks and neuraxial analgesia) and/or medications such as acetaminophen, steroids, gabapentin/pregabalin, NSAIDs, dexmedetomidine, intravenous lidocaine, COX-2 inhibitors, or ketamine. Recently, Cozowicz et al. [35] demonstrated that this approach was correlated with a reduction in opioid use, postoperative complications, and less resource utilization. Again, multimodal analgesia may reduce the occurrence of PSCP, even when expressed as postsurgery pain syndrome [36], although the link between perioperative analgesic modes and the postoperative chronitization of pain should be better investigated [37]. The challenge of the OFA or the opioid-sparing regimens remains the choice of medication pathway in terms of number, the timing of use, and doses useful in different patient subgroups. While the use of a single drug (e.g., intravenous acetaminophen or methylprednisolone) was not associated with decreased opioids consumption [38], complex regimens featuring numerous medications may only increase drug-related side effects without improving outcomes.

2.2 Chronic cancer pain: beyond the analgesic ladder

In 1986, the World Health Organization (WHO) developed the classic three-step ladder model based on the use of analgesics for pain management in accordance with pain intensity in a linear movement directed toward the high or low steps of the ladder [39]. Subsequently, it was proposed a further step concerning interventional methods such as neurosurgical procedures (e.g., neuromodulation, nerve blocks, brain stimulators, and nerve lysis) robustly recommended for managing persistent pain even following the use of strong opioids. This revised four-step path can be adopted in a bidirectional way on the basis of the type of pain and its intensity [40]. Other attempts to modify the ladder strategy have also been proposed. According to the neuromatrix theory, chronic pain represents a multidimensional experience induced by the activation of a neural network ("neurosignature patterns") extensively distributed in the CNS [41]. From these premises, Leung hypothetically revised the original analgesic WHO ladder into a new analgesic path illustrated as a platform [42]. In this model, pain management followed a three-dimensional perspective including different areas of expertise

that, in a multimodal fashion, can be combined with classical analgesics, on the basis of the pain condition. Despite its novelty, Leung's system seems to be lacking in completeness because it does not consider the dynamic perspective. The Cuomo et al. [43] "trolley analgesic model" is focused on individualized tailored therapies with dynamic multimodal approaches which are modulated according to the pain intensity, the physiopathology of pain, the multiplicity of symptoms, the presence of comorbidities, and psychological status and the patient's social context. The pharmacological agents and the nonpharmacological methods are included in different drawers of the trolley. It is possible to draw on one, or more, drawers of the trolley, and to choose within the contents of each drawer the most useful therapeutic method. According to the patient's needs, therapists can close or open different drawers, in a dynamic fashion.

2.3 Chronic non-cancer pain: toward a winning strategy

Chronic non-cancer pain conditions such as low back pain (LBP), osteoarthritis, headache, and neuropathic pain represent a significant problem in terms of psychosocial and socioeconomic consequences [44]. Due to the complexity of clinical features and multiple underlying mechanisms, this issue requires a multimodal approach. Since the 1980s, Kohles et al. [45] proposed a combined (multimodal) strategy focused on medical, behavioral, physical, and educational programs. Through this approach, defined as "functional restoration," the restoring of physical and psychological performances was obtained by the involvement of a multidisciplinary team composed of clinicians from a variety of medical disciplines (e.g., pain therapists, neurologists, orthopedics, rheumatologists), psychologists and psychiatrists, nurses, physical, and occupational therapists [46]. More recently, a task force of the German International Association for the Study of Pain (IASP) chapter has defined the principles of this approach, in terms of resources and operating methods [47]. Currently, the multimodal path has been widely recognized as winning strategy for addressing several chronic non-cancer pain conditions such as LBP, headache, and fibromyalgia although several obstacles still limit its routinely clinical application [48].

3. Conclusion

Multimodal approaches through the combined use of multiple modalities in analgesic protocols have the potential to offer a significant improvement in pain management for different acute, or chronic, clinical settings. Concerning perioperative pain management, included or not among ERAS or OFA pathways, multimodal modes can allow reducing opioid use, opioid prescriptions, and common opioid-related side effects, improving, in turn, outcomes. It seems that multimodal pain management may be able to prevent the development of chronic postsurgical pain conditions. Moreover, different attempts to better frame chronic pain in its many components, and for an effective treatment through a holistic approach, are being made to address the matter. Thus, the combined use of multiple modalities in analgesic protocols is worldwide encouraged. However, further research is needed to evaluate optimal multimodal regimens in terms of medications, doses, and timing (including the duration) of the administration, as well as to offer data useful for evidence-based practice. Finally, because lack of training (e.g., for invasive techniques or new techniques in regional anesthesia) and poor sources are huge obstacles for a routine application of multimodal approaches, identification of key barriers for their implementation seems to be a research priority.

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