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THE COMPLEXITY OF MAJOR BURN PAIN, TOLERANCE AND OPIOID-INDUCED HYPERALGESIA: A NARRATIVE REVIEW

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Abstract: Analgesia for burn patients is often prescribed with opioids at significantly longer and longer doses and durations than analgesic dosing guidelines suggest. However, many patients remain without pain relief. There is also a high risk of developing dependence and opioid use disorder such as hyperalgesia and tolerance. In addition, acute metabolic changes, exacerbated inflammatory cascades, and fluid changes associated with major thermal injuries create significant changes in the volume of distribution and pharmacokinetics of opioids in burn patients. Given these individual and unpredictable variables for each patient and the limited therapeutic windows of these agents, it is evident that pain and opioids require continuous assessment and adjustments for safe and effective pain control in this population, based on dose-response.
Keywords: "BURN", "PAIN", "TOLERANCE", "OPIOIDS", "HYPERALGESIA".

INTRODUCTION

The opioid class has been a fundamental analgesic pillar for the management of patients with severe burns (ROMANOWSKI KS , 2020). Its dose-dependent side effect profile associated with its high potential to promote tolerance and hyperalgesia limit the dose increase for acute procedural pain (MAANI CV, 2011).

The local therapeutic routine and the recovery of burn patients is exhausting due to the continuous pain and the need for one or more painful procedures a day, over weeks or months. In view of this, we observe that effective pharmacological treatment of pain for burn patients is especially challenging (WIBBENMEYER L, 2015).

Multimodal analgesia contemplates a combination of non-opioids and opioids with different mechanisms and sites of action. In trauma, it has been shown to successfully reduce the need for opioids, making evident the benefits that burn patients can acquire from this multimodal approach to pain management given its immense complexity and constant development of hyperalgesia and opioid-induced tolerance (WRIGHT M, 2020).

The objective of this study was to review and synthesize aspects of major burn pain and the complexity of the pillars that form its central and peripheral pathophysiology, in addition to emphasizing the importance of reducing opioids in its treatment and consequently of its side effects such as tolerance, hyperalgesia , dependence and immunosuppression. Proper pain management in the burned population, as a result of reducing the development of hyperalgesia and iatrogenic tolerance, demonstrates a direct impact on patient well-being and on reducing the development of chronic pain, PTSD (post-traumatic stress disorder), major depression, delirium and length of hospital stay, thus becoming a major challenge in the practice of intensive care.

THE MULTIFACTORIAL NATURE OF BURN PAIN

Burn pain is an important public health problem and despite the great improvement in the treatment of burn injuries in recent decades, we are still far from the ideal pain management for this patient. As an unintended consequence of this inefficient management, a significant number of patients have survived serious injuries and face intense pain that is very difficult to treat throughout the healing process and hospital stay. (EMERY MA, 2019)

Pain is defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage" being corroborated by the World Health Organization (ROMANOWSKI KS , 2020). Therefore, it is important to see pain as a

deep, complex and multifaceted phenomenon that has subjective, physiological and psychosocial pillars.

Pain can be described in terms such as acute or chronic in terms of time of experience and transduction pathways; nociceptive, neuropathic, somatogenic and psychogenic in relation to stimuli. In general, acute pain is the physiological and psychological response to nociception. When we talk about burn-induced pain symptoms, we must keep in mind the damage to peripheral sensory neurons and the inflammatory cascade that starts from the injury. These exacerbate the acute response and consolidate pain into a symptom complex comprising multiple components.

Inflammatory responses begin within minutes of injury and last for days . This inflammatory soup of irritating chemicals causes continuous sensitization and stimulation of peripheral pain C and A fibers throughout the initial phase of the burn. This windup mechanism includes the activation of descending facilitatory pathways from higher centers and the enhancement of the excitatory response in the dorsal horn centered on the N-methyl-D-aspartate receptor system, known as NMDA (HOLTMAN JR, 2012).

The multifactorial mechanisms of burn pain – damage to various tissues, vasculature, nerves and the exacerbated inflammatory cascade, can lead to both nociceptive pain and neuropathic pain and primary hyperalgesia (WRIGHT M, 2020). Burn injuries are reported as the most painful trauma a patient can suffer (KIM DE, 2019).

THE NEUROPHYSIOLOGY OF PAIN IN THE CRITICALLY ILL PATIENT

The free endings of nonspecific nerve fibers that are present in the skin, subcutaneous tissue, bone, muscle and viscera are afferent nociceptors that act as specialized sensory receptors in the perception of tissue trauma from thermal, mechanical and chemical sources (GARRETT N, 1999).

While transduction of the acute pain impulse occurs, tissue damage causes the release of intracellular inflammatory mediators such as bradykinin, histamine, serotonin, substance P, prostaglandins, and other cytokines. (GIUSTINO VARASSI, 2018). This release is responsible for local vasodilation, diapedesis of new inflammatory mediators, leukocyte and platelet complexes. Such cytokines promote the sensitization of other nociceptors in the affected region, which increases their excitability (JAMES DL, 2017).

Excitatory neurotransmitters associated with substance P direct the nociceptive impulse to the brain, while inhibitory neurotransmitters and endogenous opioids act by trying to inhibit nociceptive transmission and thus promoting a regulation of these impulses (WOOLF CJ, 2000).

Nerve axons, nerve impulses travel to the dorsal horn of the spinal cord, where they trigger the release of inhibitory and excitatory neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate aspartate; neuropeptides such as endogenous opioids and substance P (JAMES DL, 2017). When the impulse reaches higher structures, such as the cortical and limbic systems, the signal is then perceived as pain.

In response to all this local and systemic stress created by pain, cortisol, catecholamines and glucagon are released (BASBAUM AI, 1999). If there is no reduction in these hormones, clinically we will notice tachycardia, hypertension, increased myocardial oxygen demand, hyperglycemia, insulin resistance and alteration in the metabolism of fats and proteins (CLARK AN, 2013). Stress associated with inadequately treated pain can also lead to systemic coagulopathies and

immunosuppression of innate and adaptive systems.

OPIOID-INDUCED HYPERALGESIA AND TOLERANCE IN THE MAJOR BURN PATIENT

Increased use of opiates at any dosage was shown to be closely related to increased pain and the need for higher doses of opiates, even after controlling for baseline and procedural pain scores, burn size, and other relevant variables, reflecting thus, a tolerance effect (WIBBENMEYER L, 2015).

The expression levels of receptor, signaling and effector molecules in the dorsal horn of the spinal cord are also altered. These changes could explain the reduced potency of opioids. Concurrent with the burn injury, there is a profound change in the functional status of the immune system (EMERY MA, 2019).

Opioids have been shown to be NMDA agonists, causing activation of N-methyl-D-aspartate, which may be linked to paradoxical nociceptive stimulation (OHI) and opioid tolerance (REARDON DP, 2015). It is important to remember that although tolerance to the analgesic effects of opioids does occur, tolerance to certain side effects does not develop.

When faced with tolerance to analgesia, it is usually possible to overcome it by increasing the opioid dose . On the other hand , if the patient is under OIH, an increase in the opioid dose would result in greater pain sensitivity in the absence of disease progression. Just decreasing the amount of opioid will actually provide pain improvement (CARULLO V, 2015).

These situations are a major problem in the burn patient population, in which dressing changes and debridement are a necessary part of the treatment regimen and which require significant additional intermittent doses of short-acting opioids in the standard protocol for long periods of hospitalization. in hospital, in addition to continuous basal analgesia (HOLTMAN JR, 2012).

Ketamine is a pharmacological analgesic, which works by reducing the transmission of neural nociceptive signals through non-competitive antagonism of the N-methyl-D-aspartic acid (NMDA) receptor, as well as interactions with other receptors, including opioids, muscarinics, monoaminergics. and voltage sensitive calcium channels (MAANI CV, 2011). In contrast, remifentanil , despite being safe and effective both as an adjuvant and as a monotherapy, has been shown to be highly associated with the development of OIH, regardless of dose (ROMANOWSKI KS, 2020).

Given so many studies and preclinical trials available which directly implicate the glutaminergic system and the pathological activation of N-methyl-D-aspartate (NMDA) receptors in the development of central sensitization, the use of ketamine and methadone may attenuate this response by their NMDA antagonism. For this reason, patients who are likely to require long-term opioids are advised, when possible, to use methadone as a first-line opioid, particularly when there is a strong hyperalgic and neuropathic component to their pain. Studies indicate that the rotation of opioids to methadone and the use of ketamine as adjuvant analgesia leads to a marked improvement in the patient's hyperalgesic condition. (CARULLO V, 2015).

OPIOID-INDUCED HYPERALGESIA AND ITS MECHANISMS OF ACTION

The mechanisms of OIH are not well understood to date, but we can consider from evidence several changes in central and peripheral nociceptive pathways and, as a consequence, the activation of pro-

nociceptive processes throughout the nervous system (HOLTMAN JR, 2012).

The role of the glutamate system in the spine plays an important role in OIH and the spinal glutamate transporter has also been linked, as demonstrated by its downregulation with chronic morphine administration. It should be pointed out the important role of glutamate in the development of OIH, through its NMDA receptor and LTP. NMDA receptors are worth mentioning as their antagonists have been shown to block OIH in several studies (SHAH M, 2017).

As coordinators of peripheral neuroinflammatory processes and protagonists in the development of brain neuroinflammation , mast cells are not the only cells of the immune system on which opioids exert their action. In response to chronic morphine exposure, microglia change their structure from a branched form, characteristic of a resting state, to an amoeboid form, accompanied by upregulation of cell surface markers CD11b and ionized calcium-binding adapter-1 (SHAH M, 2017).

In view of the other neuronal pathways involved in OIH, activation of MOR or neuronal TLR4 by morphine binding deserves attention, as it will activate pro-inflammatory cascades and attempt to regulate the mechanisms involved by activating mTOR signaling , participating in neuroexcitation and OIH. Morphine can also act as an antagonist of the EEAC1 glutamate transporter involved in the recapture of this neurohormone , blocking it and thus increasing the synaptic concentrations of glutamate (ROECKEL, 2016).

Other factors are involved, such as TrkB , the BDNF receptor, which will decrease the action of KCC2 channels, which modulates Cl anion homeostasis in the snc , leading to a change in the role of GABA from inhibitory to excitatory and thus contributing significantly for the initiation and perpetuation of opioid-induced hyperalgesia (SHAH M, 2017).

FINAL CONSIDERATIONS

Therefore, for the proper management of patients with severe burns, it is essential to keep in mind the profile of dose-dependent side effects associated with the use of opioids and their high potential to promote tolerance and hyperalgesia, making use of the analgesic approach of other pillars of the development of the disease. pain, thus optimizing non-opioid adjuvant analgesia.

Acute metabolic changes and fluid changes associated with major thermal injuries create significant changes in the accumulation, volume of distribution, and pharmacokinetics of opioids in burn patients and should be basic knowledge of the intensivist. Given these individual pharmacokinetic and pharmacodynamic variables, it is evident that pain and opioids require continuous assessment and adjustments for safe and effective pain control in this population, always based on dose-response.

Mast cells act by releasing several mediators, including pro-inflammatory cytokines such as tryptase and substance P, which act directly on nerve endings, further activating and inducing SP release. Through this positive feedback in an autocrine / paracrine manner, SP causes an increase in mast cell activation to amplify the release of the mediator, thus potentiating the inflammatory cascade, the perception and processing of pain signals. It is critical to emphasize that although tolerance to the analgesic effects of opioids does occur, tolerance to certain side effects does not develop .

The role of glutamate in the development of OIH, through its NMDA receptor and LTP should also receive special attention. NMDA receptors are worth mentioning, as their

antagonists have been shown to block OIH in several studies and are excellent alternatives in the management of this patient.

Therefore, the importance of adequate analgesic management covering all pillars of pain and in a multimodal way is evident, in order to avoid the excessive use of opioids and the development of OIH and tolerance, preventing the possible transformation of this acute pain into chronic, aiming for the experience lived by the patient to be as less traumatic as possible, throughout their recovery.

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