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RESEARCH ARTICLE

PHYSIOLOGICAL MECHANISMS OF THE DEVELOPMENT OF PAIN IN BURN

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ABSTRACT

Burns are skin injuries caused by contact with hot bodies. This contact triggers lesion in skin receptors characterized by denervation, development of hyperalgesia and disorganized depolarization, depending on the extent and depth of the burn, the pain may be of greater or lesser intensity. 100% of burn patients report pain at some point during their hospitalization, either from the moment of their injury and / or during some of the treatment phases, which can be divided as follows.

- The acute phase is produced by the initial injury, which is characterized by the loss of the skin surface and is exacerbated during treatment with healing and / or surgery.
- Subacute phase. Generated during the physical rehabilitation period which is generated secondary to muscle contractures and joint ankylosis.
- The chronic phase secondary to acquired hyperalgesia, neuropathic pain due to receptor sensitization, itching and phantom limb pain in amputees.

Pain management in burned patients is essential, since it significantly reduces the development of anxiety, improves mood, avoids cardiovascular complications, etc. The timely intervention of a neuromodulatory therapy will decrease the incidence of neuropathic pain that will lead patients to the development of chronic pain. At present, pain management in burns is undervalued and pain management is sometimes deficient. One of the explanations for this phenomenon is the lack of knowledge of the neurophysiology of pain, of therapeutic management, and of the complications associated with the use of drugs such as opioids. The objective of this work is to make known to the medical staff which are the signaling pathways involved in the generation of pain in severe burns, the pathophysiology of the injury and which are the strategies they can use to reduce pain.

INTRODUCTION

The mechanisms that cause and perpetuate pain in burned patients are complex, the pathophysiological effects present different stages of evolution, in order to generate aggressive and early management strategies, and with a multidisciplinary approach to pain treatment are necessary. Severely burned patients enter a state of "burn shock," characterized by poor tissue perfusion, presence of capillary leakage, coagulopathy, and generalized release of inflammatory mediators. (2) Injuries caused by thermal burns cause immediate pain due to stimulation of local nociceptors in the skin. Pain transmits along three neuronal pathways from the periphery to the cerebral cortex. First-order neurons transmit nociceptive signals through Aδ and C fibers to the dorsal horn of the spinal cord. (1)

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Nociceptor pathways are nonspecialized naked nerve cell endings located in peripheral tissue and in the viscera that initiate nociception. or pain. Cell bodies arise in the dorsal horn of the spinal cord and send one axonal process to the periphery and the other to the spinal cord or brainstem. The ascending pathways transmit nociceptive stimuli from the periphery to the spinal cord to the brainstem (medulla and midbrain), the amygdala, the thalamus, and the primary and secondary sensory cortices (Figure.2) The descending nociceptive pathways begin in the sensory cortex and project to the hypothalamus and amygdala. The projections of the synapse of the hypothalamus and the amygdala in the periaqueductal gray in the midbrain, and the nucleus of the solitary tracts and the rostral ventral medulla in the medulla. The periaqueductal gray projects into the spinal cord primarily through the ventral rostral cord. The descending pathways are immediately activated by the ascending nociceptive pathways and the transmission of modulated noxious information (upregulate and downregulate) (18)

NEUROPHYSIOLOGY OF PAIN IN BURN

The skin contains nociceptors that respond to heat and mechanical and chemical stimulation, these receptors interpret temperatures above 42 ° C, the mechanoreceptors respond to changes caused by physical interactions, such as vibration pressure, endogenous chemical nociceptors, such as those released during the inflammatory process (histamine, leukotrienes, and substance P). [(7)] Nociception in severe burns begins with local and systemic inflammation characterized by vascular release of lipid agonists and release of cytokines by cells of immune cells are associated with the activation of TRPV1 and TRPA1 (transient potential receptor ankyrin 1) in peripheral nociceptive neurons. These first-order neurons synapse with second-order neurons in the dorsal horn of the spinal cord, which synapse with ascending neurons within the spinothalamic tract. These neurons are sensitized by astrocytes and microglia. Spinothalamic neurons terminate in the thalamus and then synapse to neurons that travel to the somatosensory cortex. The transmission of nociceptive stimuli to the cortex is modulated by descending inhibitory neurons [(3)] (Figure. 1)

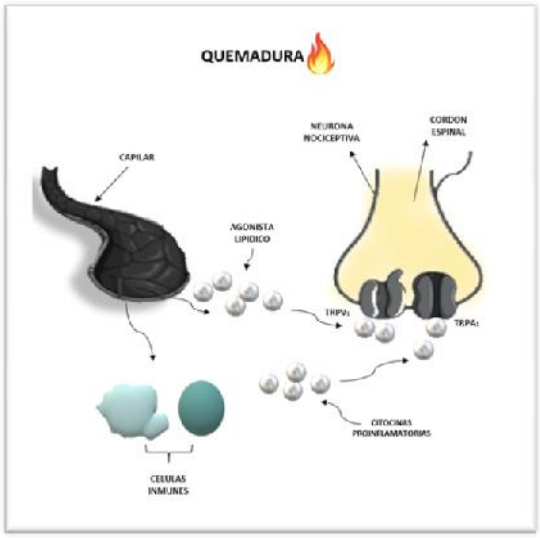

Figure 1. Nociception in injury due to burn and signaling of pain

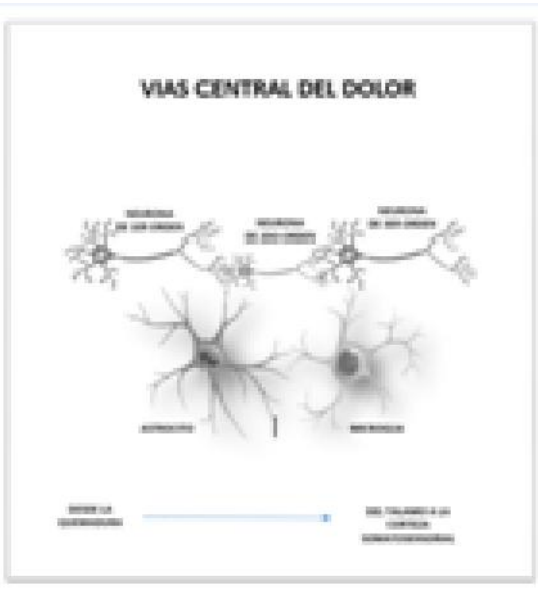

Figure 2. Central Pathway of Pain

It is known that the numerous procedures to treat burns produce intense, repetitive and prolonged painful stimuli, giving rise to the pathological alteration of the function of perception, transmission and modulation of the nociceptive stimulus, thereby achieving the amplification of the receptive areas and to the alteration of the relationship between the intensity of the painful stimulus and the response to pain.[(3)]

Opioid analgesia, tolerance and hyperalgesia by opioids: Opioids are drugs frequently used in pain control, and this is independent of patient factors. They provide effective analgesia for critically all patients. They should be used with caution as they are associated with side effects, such as sedation, nausea, constipation, and tachyphylaxis. Another consideration with its use is that critical illness induces tolerance to opioids through multiple pro-inflammatory mechanisms, including hardening of the controlled blood-brain barrier P-glycoprotein, increased circulating levels of opioid-binding glycoprotein a-1, induction Of opioid metabolizing cytochrome P450, hyperalgesic increased concentrations of opioid metabolites, increased interneuronal protein kinase and N-methyl-daspartate (NMDA) concentrations, and persistent immune activation of the dorsal horn of the spinal cord by PAMP and DAMP released after tissue damage. These changes lead to a significant increase in dose to achieve adequate analgesia. Burning directly reduces the anti-nociceptive effects of opiates in animal models, and there are reports of increases in pain associated with opioid use in burn patients, termed hyperalgesia. Some strategies to avoid opioid tolerance and hyperalgesia include:

- Decrease prolonged sedation
- Consider neuraxial anesthesia and non-neuraxial analgesia
- Rotation of opioids.
- use of multimodal analgesia with evidence to support the addition of clonidine and ketamine, as well as methadone and dexmedetomidine. However, clonidine and dexmedetomidine can precipitate hypotension in the hypovolemic patient, so it should be avoided if the patient presents with this condition.[(3)]
- Use of neuromodulators early.
- Non-pharmacological alternatives such as music therapy, hypnosis, virtual reality, etc.

Normal opioid receptor activation: During early treatment, opioids such as fentanyl and morphine bind to their receptors on the cell wall of peripheral and central neurons. The opioid receptor is coupled with G proteins, which are composed of Gabc subunits. These subunits inhibit calcium channels and activate potassium channels that lead to hyperpolarization of the neuronal membrane. The subunits also inhibit downstream AC enzymes, which decrease levels of cyclic adenosine monophosphate. In the short term, these events reduce excitability and nociception and produce analgesic effects.

Desencitisation of the receptor opioid: Through the decreased activation of the higher pain centers. However, after repeated exposure, particularly to morphine, opioid receptors become a substrate for G-protein coupled receptor kinase (GRK), leading to the recruitment and binding of the b-arrestin protein to the receptor. Opioid receptors are then less responsive to opioids and are degraded, leading to fewer less sensitive opioid receptors, therefore higher doses are required to achieve the same effect on pain Major intracellular events associated with this phenomenon in burn patients include

increased AC activity (which increases levels of cyclic adenosine monophosphate), increased phosphorylation by protein kinases (PK) and increased regulation of N-methyl-D-aspartate (NMDA) receptors. CA, adenylate cyclase. [4] Thermal hyperalgesia is nociceptive amplification that makes burns intensely painful. It is due to the excitatory modulator system of pain, existing in all the synapses of the nociceptive pathway, mainly in those neurons that use calcium channels to regulate their response threshold and generate a propagated impulse. This can be primary and secondary (Figure 3)

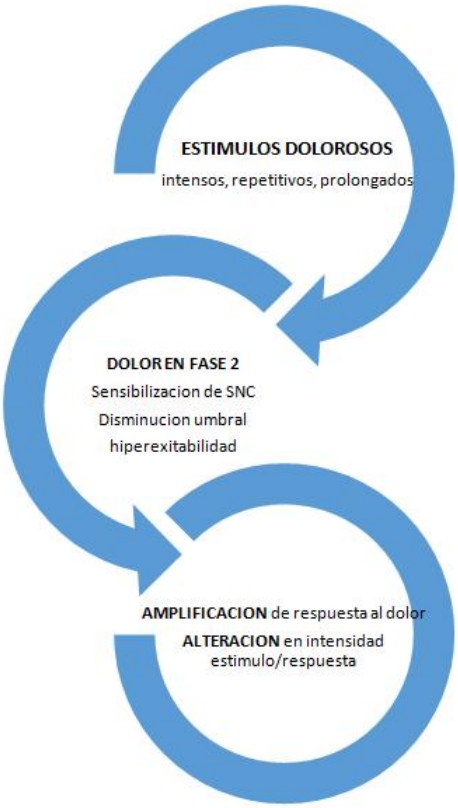

Figure 3. Amplification of the pain response

Primary: Phenomenon by which painful stimuli produce an increase in the painful response in the area of the burn. It is a manifestation of peripheral and central sensitization. Primary thermal hyperalgesia is mediated by sensitization of C-fiber thermal mechanoreceptors and type I delta A-fiber thermal mechanoreceptors, producing spinal sensitization via the NMDA receptor system.

Secondary: It refers to the pain that painful stimuli produce in undamaged peri-lesion areas, it is due to central sensitization. [17]

TREATMENT: Pain management strategies should be pharmacological (opioids first, but also non-opioid drugs to reduce side effects of the former) and non-pharmacological (hypnosis, virtual reality, cognitive interventions, distraction techniques) [5]

PHARMACOLOGICAL THERAPY: Control of burn pain is essential for the recovery and reintegration of patients with burn injuries. Poor pain control can hinder the healing process due to increased stress hormones induced by fear and anxiety (such as glucocorticoids). This can lead to physical and psychological burdens and prolonged hospital stays.

OPIOIDS: Opioids continue to be the mainstay of treatment, especially in the acute phase of burn pain, and are the most effective medication in perioperative, moderate and severe pain management. There are a variety of routes (oral, intravenous, transdermal, sublingual, rectal) and formulations (short-acting, long-acting), which allow flexibility of administration. Opioids were thought to have no ceiling effect, therefore it can be escalated to a therapeutic effect unless the side effects prevent further escalation of the dose. Unlike other analgesics, opioids do not lead to renal dysfunction or liver dysfunction, although the choice of agent and dosage should include consideration of the patient's comorbidities. Opioids, however, can cause a multitude of side effects, effects that are often dose related. These range from simply annoying effects, such as constipation, nausea, and itching, to severe effects, such as respiratory depression that leads to death. Respiratory side effects can be especially pronounced in patients with pre-existing conditions, such as sleep apnea, pulmonary comorbidities, and obesity. The incidence of side effects in patients managed for acute pain with opioids is high. [7]

NON-OPIOID ANALGESICS

Acetaminophen: Paracetamol is an antipyretic and analgesic for central and peripheral pain with modulating activity. The mechanism of action of paracetamol is unknown, but may involve inhibition of central prostaglandin synthesis, activation of descending serotonergic pathways, and inhibition of cyclooxygenase activity can be administered as first-line treatment of minor burns and as a supplement to opioids for major burns as it has a synergistic effect. [1] These medications can reduce the amount of opioids needed by 20-30%. [7]

Anticonvulsants: Pregabalin and gabapentin are anticonvulsants used in the treatment of neuropathic pain in patients with burn injuries. A 2010 case series established the efficacy of pregabalin in reducing the post-burn neuropathic pain score of outpatients. [8] Another randomized post-trial control demonstrated the role of pregabalin in both the acute phase and healing phases of burn injury, [9] [10] demonstrating reductions in neuropathic pain during the first four weeks of treatment, while additionally there was a reduction in pain levels during pain events during procedures. Another study found that pregablin had positive effects in reducing post-burn itch, suggesting that pregabalin can be used in any patient with moderate to severe itching. [9] Secondary to this, a recommendation was made to use pregabalin in mild itching to achieve the benefit of rapid and complete response.

Antidepressants: Antidepressant medications are gaining recognition for their role as part of a multimodal treatment in chronic pain. The class of antidepressants most recognized for their analgesic properties in chronic neuropathic pain states are the tricyclic antidepressants (TCAs) and the serotonin and norepinephrine receptor inhibitors (SNRIs).

Of the TCAs, amitriptyline and nortriptyline are the most widely used agents for pain. SNRIs include duloxetine, milnacipran, and venlafaxine. The analgesic effect of antidepressants does not correlate with the treatment of depression. In fact, for TCAs the analgesic benefit occurs before the anticipated effect on mood (approximately 2 weeks for pain vs. 6-8 weeks for mood). It should be noted that antidepressants cannot be used for acute pain control because their dose may need to be titrated and adjusted slowly to

minimize side effects. Additionally, the doses used for analgesia are typically lower than those used to treat a mood disorder, and serum levels do not correlate with the degree of analgesia. [7]

Non-Steroidal Anti-Inflammatory Drugs: They are potent anti-inflammatory drugs with a mechanism of action that is generally believed to be through inhibition of the enzymes that synthesize prostaglandin. However, for patients with acute burns it is limited by side effects such as gastric ulceration and kidney failure. Their use can reduce the amount of opioid needed by up to 20% to 30% because these drugs act synergistically with opioids. [7]

NMDA receptor antagonist: Ketamine is a dissociative anesthetic when used in doses greater than 1 mg ` kg, at doses lower than 0.1mg / kg, ketamine is an effective analgesic for patients showing poor response to opiates. Ketamine acts on thalamic function and on the limbic system as a potent and non-competitive NMDA receptor antagonist and inhibits the central pathway associated with central pain sensitization. Ketamine is widely used in the care of burn patients due to its pharmacological profile: it is catecholamine - sparing and it is an effective analgesic. Against neuropathic pain, opioid-induced hyperalgesia, and secondary hyperalgesia. Reduces opioid requirements by 30% in the postoperative period when used at a dose of 0.1 mg / kg / hour preserves cardiovascular stability, promotes intestinal motility, and maintains spontaneous respiration. [1]

Sedatives and anxiolytics: Benzodiazepines do not have analgesic properties, but are widely used in burn patients as adjuncts to pain management. [6] Benzodiazepines have many side effects, including respiratory ones Depression, physiological addiction, and rapid development of tolerance.36 Benzodiazepines need careful monitoring when used, but are effective supplements to opioids as they reduce distress in burn patients. [1]

Dexmedetomidine: Dexmedetomidine acts as an agonist of the pre-synaptic α-2 receptors of subtype 2A, this being more selective than clonidine. has been administered intranasally (2 μg · kg-1) with results comparable to the use of midazolam (0.5 mg · kg-1) as premedication, Dexmedetomidine also reduces the requirement for anesthetics, sedatives and analgesics, dexmedetomidine has been reported to decrease the requirement of opioids and propofol by 50 to 60% and 86% is a good supplement to ketamine, as it attenuates cardiac activity induced by ketamine stimulation and prevents delirium. [1]

Clonidine: Clonidine is an α-2 agonist used for its sedative, anxiolytic, and analgesic properties. Analgesia occurs by stimulating the descending inhibitory system, recruiting neuromediators that modulate pain perception and inhibit the release of substance P. [1] Clonidine can be used as a sole agent for analgesia, but has been associated with hypotension. Clonidine is useful as a supplement since it improves opioid analgesia, decreases the need for opioids, and prolongs the local anesthetic action, [1] it can also be administered in the management of alcohol, opiates and nicotine withdrawal. [11] In the critical care area, Pichot et al found many beneficial effects of clonidine: sedation combined with excitability, preservation of impulse airways, improvement of left ventricular performance, suppression of delirium, reduction of protein metabolism, preservation of function renal function and improvement of tissue perfusion. To obtain such beneficial effects, clonidine was administered as a slow intravenous infusion with avoidance of boluses.[12]

Cannabinoids: Nabilone is a synthetic cannabinoid, has been used as an antiemetic in patients receiving chemotherapy, and has recently been used to control neuropathic pain. The mechanism of pain modulation by nabilone is complex and involves peripheral afferent nerves, dorsal root ganglia and dorsal spinal horn, as well as specific brain areas. [13] Nabilone is effective in reducing pain and anxiety. In addition to improving sleep. [1]

Lidocaine: Lidocaine infusion has several mechanisms of action to alleviate pain, either through interaction with sodium channels or antagonistic effects on peripheral receptors such as muscarinics or glycine that enhance endogenous opioid production. Furthermore, it reduces the production of thromboxane A2, it is also often used to treat neuropathic pain, and neuropathic mechanisms are increasingly being suggested as important in pain after burns. Systemically administered lidocaine inhibits conduction in afferent nerves, along with neural transmission of the dorsal horn, and alters brain perception of pain. It is anti-inflammatory.The effect can also suppress pain. [14] Lidocaine may play a role in decreasing edema formation in burns and may reduce anxiety due to the euphoric effects of the medication. [1]

NON-PHARMACOLOGICAL THERAPY: Factors such as depression or anxiety strongly affect the perception of pain in burn patients. Agents aimed at controlling pain are important, Non-pharmacological therapies are essential adjuncts for optimal pain control. [1] Distraction is another cognitive approach based on pain control. Processing pain requires a certain amount of conscious attention and distracting such patients. Care can allow them to better tolerate pain. Movies, music therapy, and games have been used with some success as distraction techniques for burn pain. Music has the added benefit of inducing relaxation. One study found that music therapy significantly reduced pain and levels of muscle tension and anxiety before, during, and after dressing changes. [16]

Another way to distract attention is the use of augmented reality or virtual reality (VR) technology. The use of virtual reality as a powerful pain reliever has been reported in various investigations. Virtual reality can immerse patients' care in a computer-generated world and make them interact with them.These researchers indicate that virtual reality can significantly reduce pain during wound care and physical therapy.[fifteen] Hypnosis involves a mixture of relaxation, imagery, and cognitive approaches. [1], Recently, controlled studies with reliable measures of pain have endorsed hypnosis as an effective non-pharmacological approach to burn pain. [16]

Conclusions

Pain in burned patients is a very complex pathology that requires multidisciplinary support and treatment, the most ideal is a multimodal scheme to prevent or reduce hyperalgesia. It is necessary to evaluate if the patient presents pathophysiological, psychological and biochemical alterations in order to provide a better comprehensive management of the patient and achieve good analgesic management

REFERENCES

1. Retrouvey H, BSc, 2015. * Shahrokhi S, FRCSCPain and the Thermally Injured Patient — A Review of Current Therapies. *J Burn Care Res.,* 36: 315–323.
2. Kim A, Lang T, Xue M, Wijewardana A, Jackson C, Vandervord J. 2017. The role of Th-17 cells and cd T-cells in modulating the systemic inflammatory response to severe burn injury. *Int J Mol Sci.*, 18: 758-764.
3. Lang TC, Zhao R, Kim A, et al., 2019. A Critical Update of the Assessment and Acute Management of Patients with Severe Burns. Adv Wound Care (New Rochelle). 8 (12): 607–633.
4. Martyn JA, Mao J, Bittner EA. 2019. Opioid tolerance in critical illness. NEJM 380: 365–378.
5. European Burns AssociationEuropean Practice Guidelines for Burn Care Minimum Level of Burn Care Provision in Europe. Burns. 2016 Aug; 42 (5): 953-1021.
6. Wang Y, et al. 2017. Burn injury: Challenges and advances in burn wound healing, infection, pain and scarring, Adv. Drug Deliv. Rev. january; 123: 3-17
7. James DL, MD, Maryam J. 2017. MD Principles of Burn Pain Management. Clinics in Plastic Surgery, 44, (4), 737-747
8. Wong L, Turner L. 2010. Treatment of post-burn neuropathic pain: evaluation of pregablin, Burns 36 (6): 769–772.
9. Ahuja RB, Gupta GK. 2013. A four arm, double blind, randomized and placebo controlled study of pregabalin in the management of post-burn pruritus, Burns; 39 (1): 24–29.
10. Gray P, et al., 2011. Pregabalin in severe burn injury pain: a double-blind, randomized placebo-controlled trial, Pain 152 (6): 1279–1288.
11. Richardson P, Mustard L. 2009. The management of pain in the burns unit. Burns 35: 921–936.
12. Pichot C, Ghignone M, Quintin L. 2012. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? *J Intensive Care Med.*, 27: 219–237.
13. Bestard JA, Toth CC. 2011. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. *Pain Pract.*, 11: 353–368.
14. Abdelrahman I., et al., 2019. Lidocaine infusion has a 25% opioid-sparing effect on background pain after burns: A prospective, randomized, double-blind, controlled trial, Burns aviable online
15. Hoffman HG, Patterson DR, Carrougher GJ. 2000. Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: a controlled study. *Clin J Pain*., 16: 244-250.
16. Walter JM, Martyn J, Wiechman S, Christopher R. 2018. Thomas, Woodson L Management of Pain and Other Discomforts in Burned Patients. *Total Burn Care.,* 5ed: 679–699.
17. Esqueda DY, 2016. Pain management in the burn patient. *Rev. Mex. Anest.*, 39: 139-144.
18. Brown EN, Kara JP, Marusa N. 2018. Multimodal General Anesthesia: Theory and Practice. *Anesthesia-Analgesia.*, 127 (5): 1246-1258

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