Abstract
Background and objectives: Despite advances, inappropriate analgesic treatment for burn patients is still seen. The objective of this review was to collect data on pain management in burn patients.
Content: We reviewed the mechanisms of pain, burn patient assessment, as well as pharmacological and non-pharmacological treatment.
Conclusion: Pain management in burn patients is still a challenge for the multidisciplinary team. Frequent and continuous evaluation of the patient’s response is very important due to the various stages that the hospitalized burn patient goes through, as well as a combination therapy with analgesic and non-pharmacological measures. Understanding the complexity of the pathophysiological, psychological, and biochemical changes a burn patient presents is the first step to achieve success in analgesic management.

Introduction
Despite significant recent advances regarding treatment for burn victims, the inappropriate analgesic management is still seen. This is due to both the complex nature of pain presented by these patients and insufficient training of the professionals involved.

The inadequate control of pain may diminish trust within the medical team, which may negatively affect the treatment outcome. Moreover, it may contribute to the development of chronic pain, paresthesia, and dysesthesia. There is an association between insufficient pain relief and the onset of some psychiatric disorders, such as depression and post-traumatic stress disorder.

A successful treatment requires careful assessment of its nature, understanding the different types and patterns of pain and knowing the best treatment. A good initial assessment serves as a baseline to evaluate the results of subsequent interventions.

A multidisciplinary approach to these patients is critical, due to the complexity of factors involved in pain. During hospitalization, analgesia requirements vary because of the numerous procedures that patients undergo as well as their evolving condition. This makes it difficult to predict the amount of analgesic to be administered at a given time.

This review aims to present the main forms of pharmacological and non-pharmacological management of pain available in the literature.
Mechanisms of pain

The pain soon after the burn is due to direct stimulation and injury of the nociceptors present in the epidermis and dermis, which leads to the transmission of nerve impulses by A-delta and C fibers to the spinal cord dorsal horn. The impulse magnitude is modulated by both the peripheral stimuli and descending influences from the brain. The inflammatory response is initiated minutes after injury and leads to the release of numerous chemical irritants that for several days sensitize and stimulate the nociceptors at the site. The site remains painful and sensitive to mechanical and thermal stimuli, with primary hyperalgesia. The change in sensitivity to mechanical stimuli seen in the injury adjacent tissues is referred to as secondary hyperalgesia. The quality of pain changes, as the inflammatory response subsides. Pain intensity varies, but it is typically at its maximum in places of skin loss and tissue donor areas. In case of severe burns, the initial destruction of nerve endings leads to local insensitivity to pain. In these areas, there may be a disorderly regeneration of nerve tissue, which will predispose to neuropathic pain. It is estimated that up to 52% of burn patients have chronic pain.

Evaluation

It is extremely important to evaluate constantly the burn victim for pain in order to guide the analgesic management and response to drug. Characteristics, such as pain location, pain improvement or worsening, and type and intensity of pain are essential for management.

Pain intensity in this group of patients is usually assessed using a numerical scale (0-10). However, the visual analogue scale, verbal descriptive scale, and faces and colors scales are used. There are also behavioral observational scales validated for use in patients who are unable to express themselves effectively. The Abbey pain scale (for elderly with cognitive disorders) and FLACC score (for young children) are reported.

Four patterns of pain have been observed in burn patients. There may be constant pain at rest and in motion (background pain), aggravated by episodes of intense and sudden pain (breakthrough pain), pain during procedures, and pain in the postoperative period.

Pharmacological treatment

Drug administration is the primary and most effective way of treating pain in burn patients because of its nature and intensity. As mentioned previously, the inadequate management of analgesia is still very common and it is extremely important to continually reassess the effectiveness of therapy, as well as the use of more aggressive methods.

Some changes in drug pharmacokinetics are seen in burn patients. During the initial phase, when an inflammatory response develops, there is decreased blood flow to the organs, with a consequent drug clearance decrease. After this phase, there is an overall increase of metabolism with a subsequent clearance increase. In burn injuries with a body surface area greater than 20%, there is a widespread capillary leakage, with loss of interstitial proteins. Therefore, the effect of drugs with high protein binding is difficult to control. One should also be cautious with increased total body water commonly seen during treatment.

Opioids

Among the most commonly used drugs, opioids play a key role in pain management in burn patients. The variety of options available in the market allows good flexibility regarding potency, route of administration, and duration of action tailored to each patient. Its adverse effects are well-known, particularly itching, respiratory depression, and nausea. Due to the risk of tolerance or opioid-induced hyperalgesia, its use should always be incorporated into a multimodal treatment approach.

The pain at rest (background pain) present in burn patients is moderate and should be treated more appropriately with moderate potency drugs, whose plasma concentration remains relatively constant throughout the day. The most common examples are: intravenous opioid infusion, with or without patient-controlled analgesia, long-term opioids (methadone) administered orally, or prolonged enteral absorption opioids (controlled-release morphine or oxycodone). Tramadol and opioids also promote a beneficial effect in neuropathic pain. There is no evidence in literature regarding the superiority of a particular opioid for neuropathic pain. Remifentanil, an opioid with ultra rapid onset of action and plasma metabolism, is an important option for analgesia during procedures when delivered by continuous infusion. Fentanyl and alfentanil may also be used, with the advantage of promoting residual analgesia.

Anti-inflammatory drugs, paracetamol and dipyrone

These medications may reduce the amount of opioid needed by up to 20-30%. Nonsteroidal anti-inflammatory drugs (NSAIDs) may also reduce the adverse effects of opioids significantly. The most appropriate drugs for patients with burns are paracetamol, dipyrone, and selective cyclooxygenase-2 inhibitors. Although these drugs are weak when used alone, they act synergistically with opioids. Due to the inhibition of platelet aggregation, the use of NSAIDs should be avoided in situations in which risk of bleeding is a concern (such as severe burn). Its use also requires caution in patients with cardiovascular and gastrointestinal diseases.

Anticonvulsants

Gabapentin and pregabalin are often used for treating neuropathic pain in burn patients. Directly, these drugs diminish the central sensitization of pain by binding to calcium channels; indirectly, they inhibit presynaptic N-methyl-D-aspartate (NMDA) receptors. In a small study of burn patients, pain intensity and opioid consumption were significantly reduced in patients taking gabapentin. Between 3 to 24 days after the accident, patients received 2,400 mg of it, divided into three doses. In another study, pregabalin was evaluated and well-tolerated, significantly reducing several components of neuropathic pain in burn patients. Additionally, there were fewer pain complaints during procedures.
Antidepressants

Antidepressants are effective drugs and therefore play an important role in the concept of multimodal treatment of pain associated with burns. Amitriptyline, used in low doses, has an established role in the management of neuropathic pain. It acts by activating the descending inhibitory pathways in the spinal cord. The required dose is usually not more than 75 mg per day. Selective serotonin reuptake inhibitors may also be used in case of intolerance to side effects of tricyclics.

The analgesic effect of antidepressants usually occurs within days or weeks. There are no studies regarding the analgesic effect and time to start analgesic therapy in burn patients.

Ketamine

Ketamine is a non-competitive antagonist of NMDA receptors and may be used for conscious sedation during dressing changes in burn patients. It induces a state of dissociative anesthesia with intravenous doses of 1 mg.kg⁻¹. As an advantage, it maintains the airway reflexes, blood pressure, and heart rate by indirect release of norepinephrine. The occurrence of hallucinations, a significant adverse effect, may be attenuated by concomitant administration of benzodiazepines or propofol. In a meta-analysis of ketamine at low doses and postoperative consumption of opioids, the authors concluded that there is a reduction of up to one-third in total dose administered. Furthermore, ketamine was effective as rescue medication in case of pain less responsive to opioids. Ketamine appears to promote some action in reducing hyperalgesia.

Benzodiazepines

Because anxiety disorders may exacerbate pain complaints, the use of anxiolytics associated with analgesic drugs is a common practice in many centers. Fear and tension cause decreased pain tolerance. The burn patients who benefited most from therapy with benzodiazepines were those extremely anxious and with severe pain. When there is need for rapid onset of action, midazolam may be used. Lorazepam is more suitable than diazepam for this group of patients because of the decreased hepatic metabolism often present, which may prolong the half-life of the latter.

Lidocaine

Therapy with intravenous lidocaine was effective in reducing neuropathic pain scores, mainly associated with nerve injury. A clinical study, however, showed only a small difference in pain scores, requiring opioid maintenance doses during burn patients’ dressing changes.

Alpha-2 agonist

Alpha-2 agonists have interesting properties that facilitate their use in analgesic management of burn patients. Besides stimulating the descending inhibitory pain pathways, they have sedative and antihypertensive effects. Clonidine may be used safely in analgesic management of child burn victims. In some burn centers, it is routinely prescribed for children and adults. Dexmedetomidine has a shorter duration of action than clonidine and its action is more selective for alpha-2 receptors. One study reported positive results in the association between ketamine and dexmedetomidine compared to ketamine alone or in combination with midazolam during dressing changes in burn patients.

Non-pharmacological treatment

Non-pharmacological therapy is an important measure complementary to medication to manage pain and anxiety in burn patients. It should be initiated as early as possible in order to prevent the development of anxiety, which can perpetuate the cycle of pain. The approach should be multidisciplinary, involving psychologists, psychotherapists, physiotherapists and pain specialists.

Psychology techniques such as relaxation, distraction, and cognitive-behavioral therapy, are beneficial for relieving anxiety and pain during rehabilitation. Hypnosis is an altered state of consciousness characterized by increased receptivity to suggestion, ability to change perceptions and sensations, and increased capacity for dissociation. It has been used in pain management in burn patients during procedures and to control anxiety. Neurophysiological studies support this therapy.

Another approach used successfully is virtual reality. It consists of a technology that isolates the patient from the real world, letting his vision only in contact with a three-dimensional virtual environment. In the context of burn patients, this virtual world is called SnowWorld, specially created to counter sensations most commonly caused by a burn injury. In some studies, virtual reality used as a technique of distraction during procedures was effective in reducing the intensity of pain in burn patients.

Conclusion

Pain management in burn patients is still a challenge for the multidisciplinary team. Frequent and continuous evaluation of the patient’s response is very important, due to the various stages that the hospitalized burn patient goes through, as well as a combination therapy with analgesic and non-pharmacological measures. Understanding the complexity of the pathophysiological, psychological, and biochemical changes presented by a burn patient is the first step to achieve success in analgesic management.

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