Topical Analgesics

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Summary: Flores MP, Castro APCR, Nascimento JS – Topical Analgesics.

Background and objectives: Pain treatment involves the usage of common and opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvant analgesics. Traditionally, these drugs are administered systemically or into the neuraxis. However, when analgesics are applied through these pathways, they are associated with significant side effects, which can hinder its use. Topical administration of analgesics is an alternative. The objective of this paper is to discuss topical analgesics, the mechanisms of action and clinical efficacy.

Content: This is a review paper addressing the usage of the topical local anesthetics: capsaicin, clonidine, tricyclic antidepressants, ketamine, opioids and cannabinoids, discussing mechanism of action and effectiveness.

Conclusions: Topical analgesics are promising as a strategy for pain treatment, as they are associated with lower incidence of side effects. The benefit of local anesthetics, NSAID's and capsaicin is well established. However, the efficacy of clonidine, tricyclic antidepressants, ketamine, opioids and cannabinoids is still questionable. Studies have shown that the multimodal approach is an alternative, but studies are needed to confirm this hypothesis.

Keywords: Administration, Topical; Analgesia; Analgesics, Opioid; Anesthetics, Local; Antidepressive Agents, Tricyclic; Anti-inflammatory Agents; Cannabinoids; Capsaicin; Ketamine.

INTRODUCTION

Pain treatment involves the usage of common and opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and adjuvant analgesics. Traditionally, these drugs are administered systemically or into the neuraxis. However, when analgesics are applied through these pathways, they are associated with significant side effects, which can hinder its usage. Pharmacologically, it is known that the main mechanism of action of analgesics is to act at specific sites located in the central nervous system and periphery. This observation led to studies, which proposed the topical administration of drugs such as NSAID's, local anesthetics, capsaicin, tricyclic antidepressants, ketamine, clonidine, opioids, and cannabinoids. The topical application of these drugs allows high concentrations in peripheral effector sites as opposed to the low serum levels of these sites. Thus, undesirable side effects are less likely to occur. The objective of this review is to discuss topical analgesics, the mechanisms of action and clinical efficacy [1].

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TOPICAL VERSUS TRANSDERMAL APPLICATION

There are medications which are applied directly to the skin, but exert predominant effects in the central nervous system. These formulations use skinonly as a vehicle for administration, just like the fentanyl transdermal patch does. The goal is to provide a slow and gradual release of medication into the bloodstream, keeping blood levels relatively constant for a certain period of time. In contrast, topically administered medications exert peripheral effects near the site of application [1]. By definition, topical formulations are those that, when applied in the vicinity of the affected area, exert analgesic action that is associated with increased concentration in target tissue and low serum concentration.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The NSAID's are the most commonly used topical agents in clinical practice. Its mechanism of action is the inhibition of cyclooxygenase type 1 and type 2 enzymes with a consequent reduction of prostaglandin synthesis and sensitization of nerve endings in peripheral tissues, common source of pain and inflammation. Its systemic usage is associated with liver, cardiovascular, gastrointestinal and renal side effects [1]. Its topical application is interesting because it promotes therapeutic concentration in the target tissue while maintaining serum in insuficient levels to produce adverse reactions [2].

Topical NSAIDs produce high concentration in the dermis, synovium, muscle tissue, and joint cartilage, yet its bioavailability is low, ranging from 5% to 15% of that observed after systemic administration [3]. Differences in analgesic response and systemic exposure may occur depending on the source

of the pain, the type of skin and skeletal muscle tissue of each patient. There is no data correlating the systemic with the tissue concentration of the NSAIDs, so its use is still empirical based on the response of each patient. Formulations that facilitate tissue penetration may improve efficiency in deeper sites, such as joints. However, this may lead to higher systemic absorption of this group of drugs [2]. The effectiveness of topical NSAIDs for various musculoskeletal pain syndromes has been proven by several clinical trials and systematic reviews. In addition to reducing the synthesis of prostaglandins at the pain site, these drugs suppress inflammation by inhibiting leukocyte adhesion and function, reducing platelet aggregation, modulating lymphocyte response, inhibiting cytokine production, suppressing proteoglycan synthesis in cartilaginous tissue, decreasing cell lysis mediated by the complement system and inhibiting the formation of free radicals [1,2].

Recent discoveries of peripheral mechanisms involved in the pathophysiology of neuropathic pain have justified the usage of NSAIDs in patients in this condition. It is now known that nerve injury stimulates the release of phospholipids, which in turn activates phospholipase A2, generating prostaglandin E2. This product binds to primary nociceptive fibers, leading to phosphorylation of sodium channels and thereby transmitting the pain signal to the central nervous system. Therefore, this peripheral sensitization mediated by prostaglandins in primary afferent peripheral nociceptors could be blocked by NSAIDs topical agents. Topical medications such as indomethacin, aspirin and diclofenac have been used for neuropathic pain, despite the inconsistent results [4].

LOCAL ANESTHETICS

Local anesthetics applied topically can relieve pain of neuropathic origin by reducing ectopic discharges of superficial somatic nerves in areas of localized pain [4]. It binds to abnormal sodium channels, which are overregulated in damaged peripheral nerves, thereby suppressing abnormal spontaneous activity that can initiate or maintain neuropathic pain status. Local anesthetics are available as a patch containing 5% lidocaine and in an Eutectic Mixture of Local Anesthetics (EMLA) as a cream containing 2.5% prilocaine and 2.5% lidocaine [4]. In the United States, the lidocaine patch 5% is licensed for use in patients with post-herpetic neuralgia. These patches contain 750 mg of lidocaine, of which only 5% is released. Even with multiple applications of lidocaine patches, the systemic levels of this drug remain low.

Topical administration of this group of drugs has been shown to be safe and free of major side effects. A pharmacokinetic study evaluated the effects of lidocaine patch 5% applied continuously for 72 hours in healthy volunteers. The serum concentration measured was 25 times lower than that necessary to produce toxic effects. There was no loss of sensation at the site of application, but the most patients experienced mild local erythema [5].

EMLA cream has been used to provide dermal anesthesia for venipuncture, lumbar puncture, intramuscular injection, and circumcision. Some studies have explored the usage of EMLA cream in post-herpetic neuralgia, but few have shown efficacy [1]. A study of 11 patients in this condition concluded that daily application of EMLA produced significant reduction in the paroxysm of pain, allodynia, and hyperalgesia. Only one patient developed pruritus and discreet local erythema [6]. However, one should be alert to the possible onset of methemoglobinemia with the prolonged use of prilocaine [1].

Studies of the usage of lidocaine patch 5% have produced more consistent results in neuropathic pain treatment [7]. A study of 40 patients with various focal peripheral neuropathies showed a significant difference in pain scores after using lidocaine patch 5% for one week, with a Number Needed to Treat (NNT) of 4.4 for 50% pain reduction [8]. Katz et al. [9] conducted a randomized clinical trial with 332 patients with post-herpetic neuralgia. After three weeks of lidocaine patch 5%, statistically significant difference was seen in neuropathic pain scores between treatment and placebo groups: 65.8% of patients reported pain relief in the first week and 77% reported improvement in quality of life. Only 14% had mild local erythema [9].

CAPSAICIN

Capsaicin is a compound derived from a chili pepper extract. Its mechanism of action consists of binding to specific receptors/nociceptors in the skin, which initially causes a state of neuronal excitation and a period of increased local sensitivity. At this stage a burning sensation, stinging, and itching occur, associated with cutaneous vasodilation. These manifestations are attributed to the stimulation of afferent C-fibers and the release of substance P. Soon after, a refractory period occurs with reduced sensitivity, which becomes persistent after repeated applications due to the depletion of substance P and degeneration of peripheral nerve fibers [10]. This degeneration can be significant in a few days of capsaicin 0.075% usage [11]. However, with discontinuation of use, there is reinnervation of nerve fibers within six weeks (after three weeks of treatment). The potential effects of prolonged usage are unknown [12].

The adverse effects of capsaicin, which intensity depends on its concentration, result mainly from its local application and are represented by burning, stinging, and erythema. These reactions may compromise the treatment's adherence. It is estimated that for every 10 patients, one tends to abandon the treatment due to the presence of local symptoms. Moreover, due to these irritant effects, it becomes difficult to perform double-blind clinical trials with this medication. Although systemic effects are rare [10], studies have shown that some patients develop hyperreactivity of the respiratory tract by inhaling capsaicin particles.

Capsaicin is effective for treating neuropathic pain and pain associated with conditions such as osteoarthritis, rheumatoid arthritis, and psoriasis [10]. Its effect has been observed in conditions such as diabetic neuropathy, postherpetic neuralgia, chronic peripheral polyneuropathy, and surgical neuropathic pain [1]. According to a meta-analysis of randomized controlled trials, assessing the usage of capsaicin 0.075% for eight

weeks in patients with neuropathic pain there was a NNT of 6. For capsaicin 0.025% in patients with musculoskeletal pain the NNT was 8 [10].

CLONIDINE

Clonidine is a pre-synaptic α-2 adrenergic receptor agonist drug present in structures of the central and peripheral nervous system, specifically in the brain, spinal cord, and dorsal root ganglia. All these sites are potentially involved in the antinociceptive effects of clonidine. The sympatholytic action of clonitidine is known to act in the supraspinal and spinal structures, which are responsible for painful stimuli modulation, resulting in effective analgesia. Classically, clonidine has been used systemically and in the neuraxis. Its therapeutic use, however, has been limited by adverse effects such as sedation, dry mouth, hypotension, and rebound hypertension [13].

It is known that α-2 adrenergic receptors are expressed in the nociceptive primary sensory neurons and that the peripheral administration of α-2 receptor agonist produces antinociception. This observation led to the hypothesis that the topical administration of clonidine has antinociceptive effect, motivating the development of this formulation [4,13]. Clonidine, as a lipophilic substance, is believed to easily penetrate the skin and reach the local antinociceptive pathways, providing analgesia.

The damaged peripheral nerves have increased adrenergic sensitivity, and the presence of agonists, such as norepinephrine, may increase its ectopic discharges, resulting in greater pain. Studies show that the activation of peripheral α-2 adrenergic receptors by clonidine reduces the local release of catecolminas, reducing pain and allodynia [4,13].

Topical clonidine has been effective in patients with diabetic neuropathy, especially those with thin, sharp pain [14]; however, its repeated topical application may result in antinociceptive tolerance by the third day of use [13].

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants are well-established as pain medications. The effect is at the central level by inhibiting the reuptake of norepinephrine and serotonin, and activation of descending inhibitory pain pathways. The peripheral analgesic effects of tricyclic antidepressants have been attributed to the decrease of cyclic AMP via adenosine receptor activation and inhibition of the voltage-dependent sodium channels. Regarding systemic side effects, it may cause sedation, postural hypotension and anticholinergic responses [15].

The topical formulation containing 4% amitriptyline and 2% ketamine was effective in reducing neuropathic pain after three weeks of treatment [16]. The formulation containing 5%, however, was not effective, showing the importance of the association of different drugs with different mechanisms of action for better pain control [15].

Doxepin, a tricyclic antidepressant with a mechanism of action similar to that of amitriptyline, when administered in 5% formulation was effective in reducing pain after two weeks of usage in patients with neuropathic pain, oral mucositis related to cancer and complex regional pain syndrome type 1 [17-19].

KETAMINE

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. Neurotransmitters such as glutamate and aspartate are released in response to noxious stimuli and bind to NMDA, AMPA and glutamate-type M receptors, playing a significant role in the mechanism of central sensitization and wind-up phenomenon, which are involved in the perpetuation of pain. Despite its potential benefits for pain treatment, especially neuropathic pain, the systemic administration of ketamine in outpatient clinics is due to the lack of oral formulations and the adverse effects such as hallucinations, nausea and vomiting [20]. Topical ketamine gel is an alternative, as it is easy to apply and acts on opioid receptors, such as the NMDA receptor antagonist and peripheral blockade of sodium and potassium channels [21].

Topical ketamine, when administered to patients with chronic neuropathic pain is effective to reduce allodynia and hyperalgesia [21]. Studies show that the analgesic effect of ketamine is dose-dependent, with changes in thermal sensitivity, sense of relaxation and analgesia at doses of 0.13 $mg.kg^{-1}$, 0.2 $mg.kg^{-1}$, and 0.37 $mg.kg^{-1}$, respectively [20].

Topical ketamine may be a therapeutic option for patients with neuropathic pain. In patients with complex regional pain syndrome, the topical usage of ketamine was effective to improve allodynia [21]. However, due to the lack of more consistent studies involving a larger number of patients the topical usage of ketamine should be reserved for refractory cases [20].

OPIOIDS

Opioids are already established drugs for the treatment of moderate to severe pain. Potential adverse effects and fear of addiction have limited its usage. They act on specific receptors that, when activated, interfere with the transmission of pain impulses. The inhibitory effects are exerted both in the brain and by increasing the threshold of nociceptive fibers of gelatinous substance found in the dorsal horn of the spinal cord. Studies have shown that opioid receptors are also present in the peripheral nervous system. When synthesized in dorsal root ganglia of the spinal cord, these receptors are transported to the peripheral terminals of primary afferent neurons via axons, which, when stimulated, decrease the release of substance P contributing to pain control.

Based on this knowledge, opioids of topical formulation have been studied for the treatment of pain related to pressure ulcers, considering that changes in local perfusion prevent systemic opioids from achieving satisfactory levels in the desired site of action. Moreover, patients with this type of injury often have several comorbidities and are therefore more prone to the systemic adverse effects of opioids, mainly respi-

ratory depression [22]. Three randomized trials demonstrated the efficacy of morphine and diamorphine gel for treating pain related to pressure ulcers, with improvement in pain scores using verbal scales [23-25]. However, there are no clear recommendations regarding the optimal dosage and opioid [22].

Morphine oral rinse solution also has proven effective for analgesia in patients with cancer-related mucositis and the 2% solution was statistically more effective than the 1% solution [26,27].

CANNABINOIDS

Cannabinoids are substances derived from the hemp plant *Cannabis sativa*, with depressant and hallucinogenic properties. The central antinociceptive effects of cannabinoids are mediated by CB1 receptor activation in the brain and spinal cord, acting in the modulation of painful stimuli. The CB2 receptors are present in non-neural tissues, such as microglia. The systemic side effects of cannabinoids, however, can cause hypoactivity, motor dysfunction and hypothermia, which has been one of the limitations for its therapeutic usage, in addition to issues related to sociocultural and legal aspects [28].

The observation of the expression of cannabinoid receptors in peripheral neurons has contributed to the completion of works evaluating the usage of topical formulations comprising cannabinoids. Activation of CB1 receptors promotes local inhibition of cyclic AMP synthesis, inhibition of substance P and related to the peptide calcitonin gene, in addition to opening of potassium channels via G protein. Its topical analgesic effect has been demonstrated in animal models alone [29] or combined with other analgesics. It has been shown that the topical usage of cannabinoids can potentiate the antinociceptive effects of topical morphine [30].

CONCLUSION

Topical analgesics are promising as a strategy for pain treatment, as they are associated with lower incidence of side effects. The benefit of local anesthetics, NSAIDs, and capsaicin is well established; however, the efficacy of clonidine, tricyclic antidepressants, ketamine, opioids and cannabinoids is still questionable. Trials show that the multimodal approach is an alternative, but more studies are needed to confirm this hypothesis.

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