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Research Progress of Lidocaine in the Treatment of Chronic Pain

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Abstract: Chronic pain is a subjective experience that involves not only nociception but also emotional, cognitive, and social factors. Chronic pain affects almost every aspect of daily life. However, the mechanism of chronic pain is extremely complicated. Clinically, there is still a lack of safe and effective treatment methods for chronic pain, and its treatment has always been an important topic in the medical field. In recent years, more and more studies have shown that lidocaine may be an excellent analgesic. It can be used alone as a patch for external use, as a supplement to systemic medication methods, and also for optimizing the treatment of chronic pain and multimodal analgesia. This article reviews the latest research progress of lidocaine in the treatment of chronic pain.

Keywords: Lidocaine; Chronic Pain; Neuropathic Pain; Cancer Pain.

1. Introduction

Currently, modern medicine lists pain as the fifth vital sign of humans. Chronic pain is a common and complex afflictive disease, often having a huge impact on both individuals and society [1]. The International Association for the Study of Pain (IASP) has revised the definition of pain as an unpleasant sensory and emotional experience associated with or similar to actual or potential tissue damage [2]. Recurrent or persistent pain that lasts longer than the expected healing time (usually three months or more) is chronic pain [3]. Chronic pain is a leading cause of disability worldwide, and its prevalence is likely to increase in the next few decades [4]. Chronic pain affects individual families as well as society and the health - care system. However, the mechanism of chronic pain has not yet been completely understood [5], and progress in treatment has not achieved the same level as that of many chronic diseases, thus exacerbating concerns about the future burden of this disease. According to some studies, chronic pain imposes a huge individual economic burden and has a great impact on more than 30% of people worldwide [2]. Therefore, the search for drugs to effectively treat chronic pain is becoming increasingly urgent.

In 1943, Lofgren and Lundgvist first synthesized lidocaine. Compared with procaine, the most commonly used local anesthetic at that time, subsequent studies unexpectedly found that lidocaine had better anesthetic effects [6]. Since its approval for use in Sweden in 1948, lidocaine, as an amide - type local anesthetic, has long been used for topical anesthesia, infiltration anesthesia, nerve block, and dental anesthesia [7]. Then, in 1951, it was first recognized that intravenous injection of lidocaine had an analgesic effect and could effectively relieve intraoperative pain [8]. As people's understanding of the hazards of opioid drugs has deepened, there has been an increasing interest in non - opioid analgesics [9]. Lidocaine is one of the potential drugs to promote opioid - free or reduced - opioid anesthesia [10][11]. In recent years, many studies have shown that the application of lidocaine has an analgesic effect in chronic pain states and can be used in the treatment of various chronic pain conditions. In view of this, this article reviews the mechanism of action and the latest clinical studies of lidocaine in the treatment of chronic pain, hoping to provide new ideas and directions for clinical treatment.

2. Mechanism of Action

The main mechanism of action of lidocaine as a local anesthetic is the reversible blockade of the propagation of action potentials by blocking voltage - gated sodium channels [12][13][14][15]. Intravenous infusion of lidocaine has an analgesic effect in both acute and chronic pain states, especially in acute postoperative and chronic neuropathic pain [14]. The reason for its analgesic effect cannot be simply explained by the above - mentioned mechanism. To some extent, like local anesthetics, intravenous infusion of lidocaine may also act through ion channels, but it can interact with almost all ion channels [7][13][14]. This makes it very difficult to determine the specific mechanism of lidocaine in treating pain. Currently, a large number of pre - clinical study results show that lidocaine has effects on both the peripheral and central nervous systems [7][16], and its analgesic properties may be related to multiple molecular mechanisms of cellular, sub - cellular, specific - regional and systemic actions [14]. Lidocaine may play an analgesic role by inhibiting ectopic discharge of sensory nerves, inhibiting inflammatory reactions, and regulating the release of inhibitory/excitatory neurotransmitters [14][15].

2.1. Blocking Ion Channels to Inhibit Abnormal Nerve Discharges

Lidocaine can produce an analgesic effect by blocking voltage - gated sodium channels (VGSCs). VGSCs form the molecular basis of the functions of the nervous system, including sensory transmission, and thus are involved in the formation and conduction of pain signals. Multiple experimental studies have shown that intravenous injection of lidocaine can inhibit ectopic discharges in the damaged dorsal root ganglion (DRG) or peripheral nerves [17][18], which may explain one of the mechanisms of lidocaine in the clinical

treatment of chronic pain.

Potassium ion channels play a variety of physiological functions in excitable cells. In nerve transmission, potassium ion channels maintain the resting membrane potential and regulate excitability. Certain types of potassium ion channels are involved in pain regulation and may become targets for future pain treatment, especially specific voltage - gated potassium ion channels and two - pore - domain (K2P) channel families. Busserolles et al. [19] found in their research that low - concentration lidocaine inhibits tonically firing neurons by interacting with voltage - gated potassium ion channels, which may be another mechanism for lidocaine to exert its analgesic effect.

Voltage - gated calcium ion channels (VGCCs) regulate many physiological processes, including the release of neurotransmitters. Under pathological conditions, such as nerve injury, the dysregulation of VGCCs is associated with hyperalgesia. Since they have a great impact on the release of neurotransmitters, they are often considered potential targets for the treatment of chronic pain [20]. Yasuo et al. [21] studied that in the dorsal root ganglion of frogs, lidocaine can act on VGCCs to effectively inhibit their functions, thereby possibly mediating the effect on chronic pain.

2.2. Inhibition of Inflammatory Reactions

Neuroinflammation is closely related to the occurrence and development of chronic pain, and non - neuronal cells play a key role. Infiltrating and activated leukocytes and activated glial cells stimulate the production of inflammatory mediators and drive the inflammatory signal cascade, thereby leading to the activation of nociceptors [22]. Lidocaine can inhibit the activation, adhesion, and migration of leukocytes. In both in - vitro and in - vivo studies, it also protects cells from inflammatory reactions by reducing neutrophil adhesion and inhibiting the release of superoxide anions, as well as by blocking the release of inflammatory mediators to play a role in pain relief. These inflammatory mediators include interleukin (IL), tumor necrosis factor - α (TNF - α), transforming growth factor - β (TGF - β), and C - reactive protein (CRP), etc. [14][23][24][25].

All immune cells, epithelial cells, fibroblasts, and tumors can produce interleukins. The type of interleukin secreted depends on the cell type and the type of immune response. IL-1, IL-2, IL-6, IL-8, and IL-17 promote inflammatory reactions, while IL - 4 and IL - 10 are immunosuppressive or immunomodulatory [23][24][25][26]. Castro [23] and others' research results showed that during the peri - operative period, intravenous infusion of lidocaine significantly reduced the levels of IL - 1 and IL - 6 24 hours after the operation. IL - 6 is a pro - inflammatory cytokine related to surgical trauma, and its increase can also cause sensitization of the peripheral/central nervous system and then lead to hyperalgesia [23][24]. This result may support the mechanism that lidocaine has an anti - inflammatory effect and thus relieves pain. However, no significant reduction in the levels of IL - 8 and IL - 10 was observed in the meta - analysis. Nevertheless, most of the studies in the analysis reported varying degrees of decrease in the levels of IL - 8 and IL - 10, indicating that lidocaine may also have an anti - inflammatory effect on these cytokines and thus can play a certain analgesic role. In addition, similar results were also found in CRP [23].

TNF - α is an important pleiotropic cytokine involved in host defense, inflammation, and apoptosis. It plays a dual role in the regulation of the immune response. It can act as a pro - inflammatory mediator to trigger a strong inflammatory reaction, and it can also act as an immunosuppressive mediator to inhibit the development of autoimmune diseases and tumors. It also plays an important role in maintaining immune homeostasis by limiting the extent and duration of the inflammatory process. After intravenous injection of lidocaine, the level of TNF - α is significantly reduced at the end of the operation. This may be a mechanism by which lidocaine exerts an analgesic effect by inhibiting the inflammatory mediator TNF - α [23][25].

TGF - β is produced by a variety of cells, such as epithelial cells, fibroblasts, and immune cells. Transforming growth factor - β (TGF - β) is one of the main cytokines for the inhibitory function of regulatory T cells and the differentiation of pro - inflammatory helper T cell 17 (Th17) and helper T cell 9 (Th9). Most somatic cells express TGF - β receptors and can respond to TGF - β signaling. Thus, lidocaine may achieve anti - inflammatory and analgesic effects by reducing the production of TGF - β to inhibit the growth of immune cell precursors and regulate the differentiation of multiple T - helper cell subsets [23][26].

2.3. Regulation of Neurotransmitters

Glutamate is the most important excitatory neurotransmitter in the central nervous system and is closely related to pain sensation. Studies have shown that lidocaine can inhibit glutamate release from nerve endings at clinically relevant concentrations (IC50 is 45 μM) [27]. Besides directly inhibiting glutamate release, lidocaine also has an effect on glutamate transporters. Lidocaine enhances the activity of excitatory amino acid transporters mediated by PKC and phosphatidylinositol 3 - kinase, accelerates the reuptake of glutamate in the synaptic cleft, and thus reduces nociceptive pain [14][28]. Glutamate is mediated by ionotropic and metabotropic glutamate receptors. Among the ionotropic glutamate receptors, the N - methyl - D - aspartate (NMDA) receptor is inseparable from the conduction of pathological pain signals [29]. Research shows that in oocytes expressing human NMDA receptors, even nanomolar concentrations of lidocaine can inhibit NMDA - mediated currents and thus reduce nociceptive pain [14][30].

In addition, γ - aminobutyric acid (GABA) as an inhibitory neurotransmitter, especially in the spinal cord, also plays a key role in the processing of pain information. The results of rat experiments by Ikeda et al. [31] showed that intravenous infusion of lidocaine can inhibit the release of GABA, thereby reducing pain. At the same time, in vitro, lidocaine enhances GABA - mediated Cl - currents by inhibiting GABA reuptake. This may explain the analgesic effect of lidocaine, because other GABA reuptake inhibitors, such as tiagabine, have good effects on chronic pain [32]. The above research results indicate that lidocaine may play an analgesic role by regulating excitatory/inhibitory neurotransmitters.

3. Clinical Studies

3.1. Chronic Neuropathic Pain

Chronic neuropathic pain is a special type of chronic pain caused by nerve tissue lesions in the peripheral or central nervous system. It is one of the more severe types of pain and can interfere with various aspects such as sleep, work, and daily life [33]. Many patients with neuralgia may experience anger, frustration, and may even develop anxiety and depression [34]. Neuropathic pain is different from other

types of pain as it is difficult to treat. Patients usually use multiple different types of drugs, but all drugs have significant adverse reactions [17]. Currently, drugs commonly used in clinical practice for treating neuropathic pain include antidepressants (tricyclic antidepressants, serotonin, selective norepinephrine reuptake inhibitors), anticonvulsants (calcium channel antagonists: pregabalin, gabapentin; sodium channel antagonists: carbamazepine, oxcarbazepine), sodium channel blockers (lidocaine), TRPV1 agonists capsaicin, and opioid drugs [33]. Research by Zheng et al. [35] has shown that lidocaine promotes the expression of SOCS3 in microglia, and over - expression of SOCS3 can inhibit the expression and activation of p38MAPK and NF - κB stimulated by lipopolysaccharide, thereby inhibiting the aggregation of microglia and producing an effect of alleviating neuropathic pain. A retrospective study found that intravenous injection of a medium - dose of lidocaine can significantly relieve chronic intractable neuropathic pain [36]. Another retrospective study showed that a 700 - mg lidocaine patch can relieve pain and improve the quality of life of patients with post - herpetic neuralgia after 8 weeks of treatment. The lidocaine patch has good analgesic effect and few side effects, and is mainly suitable for mild to moderate chronic pain [37].

3.2. Chronic Cancer - Related Pain

Currently, cancer remains a difficult problem in the field of treatment worldwide. With the rapid development of modern oncology research and treatment techniques, the survival time of cancer patients is gradually increasing [38]. However, the resulting complications are also obstacles that need to be urgently resolved at present. Pain is one of the most common complications of cancer. Chronic cancer - related pain refers to pain caused by the primary cancer itself or by tumor metastasis eroding bone, viscera, and nerves (chronic cancer pain) or pain related to tissue or nerve damage caused by cancer surgery, chemotherapy, and radiotherapy (post - cancer - treatment chronic pain) [38]. A meta - analysis showed that compared with a placebo, infusion of 4 - 5mg/kg of lidocaine within 30 - 80 minutes may reduce cancer pain by 50%. Based on the currently available evidence, lidocaine infusion can be considered for intractable cancer pain that is refractory to level - 1 - evidence drugs [39]. A retrospective study by Ferguson et al. [40] showed that for patients for whom traditional analgesics have proven to be less than ideal, subcutaneous injection of lidocaine is a safe and effective method that can be used for palliative care to relieve complex cancer pain. However, patients may require rapid titration of opioid drugs, so the infusion process needs to be carried out in a monitored environment. In the reviewed cases, subcutaneous infusion of lidocaine improved the pain sensation and significantly reduced the daily dose of oral morphine [40]. However, another study showed that a single subcutaneous injection of 10mg/kg of lidocaine within 5.5 hours cannot achieve the expected therapeutic blood concentration to relieve chronic cancer - related pain [41].

3.3. Chronic Post - Operative or Post - traumatic Pain

Chronic post - operative or post - traumatic pain refers to pain that occurs, develops, or intensifies after tissue injury (including various traumas such as burns) and persists after healing (that is, persists for at least 3 months after surgery or tissue trauma). The pain site is often located in the trauma area or projected to the innervation area of the nerves in this area, especially after deep somatic or visceral tissue injury. It is necessary to exclude pain caused by other reasons (including infection, malignant tumors, etc.) and pain that has already existed and persisted until now [42].

The use of intravenous lidocaine for treating chronic pain and for reducing acute post - operative pain during the peri - operative period is increasing. Local anesthetics block sensory information in the spinal cord, thereby reducing sensitivity [43]. A study conducted by Grigoras et al. [44] found that intraoperative intravenous infusion of lidocaine is effective in preventing chronic pain after breast cancer surgery. Their research protocol was to inject 1.5mg/kg of lidocaine intravenously before induction of general anesthesia, and then infuse lidocaine at a rate of 1.5mg/kg·h; the control group received an equal volume of normal saline. It was found through the study that lidocaine can significantly reduce the incidence and severity of chronic post - operative pain 3 months after the operation. Lidocaine cream during the peri - operative period has also been found to reduce the incidence of chronic pain after mastectomy [43]. A clinical study by Lu et al. [45] found that peri - operative infusion of lidocaine significantly reduced the number of PCA trigger times and the incidence of chronic post - operative pain 3 months after thoracoscopic surgery.

4. Summary

In summary, the treatment of chronic pain has certain difficulties, and lidocaine can exert analgesic effects through multiple mechanisms. Current clinical studies show that lidocaine can treat various types of pain, especially for those chronic pains where traditional drugs are ineffective, lidocaine can relieve them to a certain extent. However, in view of the current quality of clinical data and the adverse reactions of lidocaine itself, a large number of long - term clinical trials are still needed for evaluation. Timely following up on the latest progress of lidocaine in treating chronic pain can provide new options for the clinical treatment of chronic pain.

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