

# Research Status of Preemptive Analgesia and its Application in Clinical Anesthesia

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**Abstract:** The most effective treatment for postoperative pain is to reduce it by preventing or reducing the sensitivity and sensory disturbance on the central nervous system during the operation, prolonging the pain-relief time and reducing the use of analgesics. Preemptive analgesia refers to the intervention of central neuraxis sensitization and peripheral sensitization to prevent the expansion and spread of pain, so as to achieve postoperative pain-relief. In postoperative patient-controlled analgesia, preemptive analgesia has become a common treatment method for anesthesiologists. However, the clinical specifications for advanced analgesia are still lacking. Based on this, this paper reviews the use of advanced analgesia drugs and their clinical applications.

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## 1 Introduction

In clinical surgery, doctors and patients always have the value of solving postoperative pain. This is because if pain cannot be effectively controlled, it may lead to a series of harmful acute and chronic consequences. Active pain-relief is preventive treatment before pain occurs. It aims to block the spread of preoperative pain, reduce pain during surgery, relieve pain after surgery, and improve the quality of life of patients. In the traditional sense, preemptive analgesia refers to the use of analgesics and other pain-relief methods before surgery<sup>[1]</sup>. In

recent years, more and more clinicians have begun to use advanced analgesia to reduce postoperative pain. Although they have achieved certain results, they have also brought new problems and challenges.

## 2 Mechanisms of preemptive analgesia

The pain caused by surgery is mainly pathological pain, including inflammatory pain and neuropathic pain. Both of them lower the pain threshold by adjusting the response of central and peripheral sensitization to pain stimuli. In order to better understand the mechanism of preemptive analgesia, it is important to understand the characteristics of preemptive analgesia. Most of the pain after surgery is inflammatory pain. Regardless of the degree of pain, usually central and peripheral sensitization can be used to adjust the pain stimulus response, thereby effectively reducing the pain threshold<sup>[2]</sup>.

### (1) Peripheral sensitization

It can cause vasodilation and tissue swelling after peripheral tissue injury, and release and produce various chemicals and cytokines, thereby causing pain-sensitization called peripheral sensitization. It mainly triggers the human body's violent response to harmful stimuli through the following mechanisms:

Tissue damage products such as H<sup>+</sup> bradykinin, prostaglandin, and histamine act on ion channel receptors of nociceptor neurons, leading to prolonged depolarization time and slow ion channel deactivation, thereby lowering the threshold of pain receptors and cause hyperalgesia. Stimulating the release of chemicals from the damaged area can cause ectopic secretion of damaged nerves, which greatly

increases the body's response to harmful stimuli and exacerbates pain. After tissue injury, immune cells are activated, immune response is enhanced, more inflammatory factors are released, resulting in more severe pain. Sympathetic nerve endings release phospholipase C and phospholipase A2 through sympathetic binding, inducing the release of Pgi1 and PGf2, and aggravate inflammatory hyperalgesia<sup>[3]</sup>.

#### (2) Central sensitization

In addition to peripheral sensitization, harmful stimuli can also increase the excitability of the central nervous system, leading to hyperalgesia or central sensitization.

**Spinal cord ganglion sensitization:** The spinal horn of the spinal cord is a relay station that transmits harmful information. After peripheral nerve injury, the amount of substance P and glutamate in afferent nerve fibers increases. This transmitter acts on the NK1 and NMDA receptors in the dorsal horn of the spinal cord, causing membrane depolarization and a large influx of  $Ca^{2+}$ . Neurons that are sensitive to pain in the dorsal spine are in a very sensitive state and can induce pain-sensitive responses. After nerve injury, brain-derived nerve growth factor (BDNF) induces inappropriate synaptic connections in the dorsal horn of the spinal cord. These new synaptic connections can cause pain-sensitive neurons to receive more afferent pulses, which can lead to hyperalgesia.

**Control the central nervous system above the spinal cord:** The central nervous system can inhibit harmful peripheral stimuli, mainly through downward inhibition and downward promotion of the brainstem. The central structure that inhibits and promotes the decline of the brainstem mainly includes: the rostral ventromedial medulla (RVM) with periaqueductal gray matter (PAG) as the core; and locus coeruleus, basal and lateral nucleus; ventral anastomosis - similar structure; outer reticular cell nucleus, the key is to inhibit and promote the reduction of PAG. The normal function of the brainstem pain control system is mainly related to norepinephrine neurons, serotonin neurons and endogenous opioid peptides. The pain signal is transmitted through the thalamus to the cerebral cortex to cause pain. Studies have shown that MD nucleus - cortex - cingulate gyrus - dIPAG column, CM caudate PF and SM-VLO-PAG pain control pathways are endogenous two-way regulatory systems that participate in and generate the recognition, integration and regulation of pain information. Downward

inhibition and promotion. Inflammation and immune system involve glial cell activation, mitogen activated protein kinase (MAPK) and P2X4 receptor<sup>[4]</sup>.

### 3 The research status of preemptive analgesia

The effectiveness of preemptive analgesia is still debatable. Clinically, preemptive analgesia is used at different times according to the mechanism of pain and different targets in the peripheral and central nervous systems. Preventive analgesics and methods mainly include the following aspects:

#### (1) Opioid drugs

The number of opioid receptors increases after tissue injury. The application of opioids can prevent substance P from binding to receptors, thereby preventing the transmission of pain information and producing analgesic effects. However, studies have shown that single-use opioids are not ideal preemptive analgesics. They can be administered as a reasonable drug for first-time pain-relief. Studies have shown that the application of sufentanil citrate preemptive pain-reliever PCIA (continuous use of analgesic pump) before debridement and skin transplantation can significantly reduce the pain during burn surgery. In some animal experiments, opioids have been shown to have anti-damage effects on opioid receptors outside the central nervous system. For example, intra-articular injection of morphine hydrochloride and different doses of morphine under arthroscope can provide good postoperative pain-relief<sup>[5]</sup>.

#### (2) Local blockade preemptive analgesia

**Local anesthesia.** Local anesthesia is the most commonly used method for first-time pain-relief, such as long-term use of ropivacaine and bupivacaine or short-acting lidocaine, which are commonly used drugs. In the process of preemptive analgesia, central nerve blockade, peripheral nerve blockade and local infiltration are usually applied, and the time of administration is optional, such as during or before surgery. Currently, people have fully understood the research data of preemptive analgesics related to topical drugs, and are comparing and confirming their analgesic effects. When preemptive analgesia is used, the anesthetic effects of long-acting ropivacaine are better than that of short-acting lidocaine. As we all know, the scope of local blockade such as local anesthesia, peripheral nerve blockade and spinal cord blockade is very wide. In general, it is believed

that preoperative site blockade can prevent central sensitization by effectively blocking harmful stimuli from entering the central nervous system.

### (3)NMDA receptor antagonist

Ketamine has been used to treat neuropathic pain or cancer pain that is insensitive to opioids. However, reports on preemptive analgesia are debatable. Opioid receptors are important targets for pain treatment. Receptor agonists can prevent inflammatory mediators from sensitizing pain receptors. Receptors are located in the sympathetic nerves, due to the release of bradykinin, the sensitization of pain receptors can be prevented. Opioids act on the spinal cord and peripheral opioid receptors to reduce pain and central and peripheral sensitization.

There are many reasons for the controversy about preemptive pain relief. The main reasons are: (1) The definition is wrong. Proactive pain should not only emphasize preoperative intervention, but also include blocking the transmission of pain signals during the entire process of harmful stimuli (including surgical incision and tissue damage, postoperative inflammatory stimulation). In some studies, the purpose of preventing sensitization cannot be achieved only when painkillers are not given before and after the operation. (2) Incomplete blocking of nociceptive afferent impulses, such as lack of a single dose before injury, lack of analgesics after surgery, or cessation of inflammation may delay postoperative pain, but it cannot effectively prevent peripheral and central causes. (3) If the intensity of the operation is low and the harmful stimuli are not enough to cause pathological pain after the operation, the preemptive analgesia effect cannot be manifested. (4) The measurement of pain scoring and analgesic dose is subjectively affected by the patient's psychological factors to a certain extent. (5) The results of opioid analgesia in advance indicate that this may be due to the phase 2 time-dependence of opioids (such as fentanyl), which increases the pain threshold in the early stage (2 to 5 hours). After the patient is feeling pain, fentanyl activates NMDA receptors to promote the process of pain, lowers the pain threshold and increases pain sensitivity<sup>[6]</sup>.

## 4 The clinical application of preemptive analgesia

Preemptive analgesia is only an analgesic method,

and its specific mechanism requires more research. The key to preemptive analgesia is not the time of administration, but the effective prevention of hyperalgesia and prevention of central and peripheral hypersensitivity. With the continuous deepening of basic and clinical research, it is believed that active pain-relief will become a complete and feasible clinical treatment method that can effectively alleviate various acute and chronic pain. The key is to prevent the introduction of all harmful stimuli before pain occurs, but the generation, conduction and regulation of pain is a very complex process involving multiple specific receptors, specific pain pathways and various inflammatory mediators. Therefore, the combination of multiple analgesia methods and drugs (ie, multimodal preemptive analgesics) can better prevent harmful stimuli and achieve better analgesic effects, such as:

### (1)Mainly used for pathological pain

Inflammatory and neuropathic postoperative pain are caused by inflammation caused by damage to peripheral tissues, including wound pain irritation, non-pain irritation and spontaneous pain in the inflamed area. Peripheral and central nervous system hypersensitivity are related to pain stimulation. Central sensitization usually lasts for a long time, from a few hours to a few weeks. Peripheral sensitization is limited to the initial stage of trauma, and the sensitive period of abnormal pain is longer. In order to achieve sufficient and effective analgesia, it is necessary to actively relieve pain before trauma and apply it to wound healing to completely inhibit peripheral and central nervous system hypersensitivity.

### (2)Time and methods of pain-relief

Preoperative, intraoperative and postoperative special factors can cause postoperative pain, especially: ① preoperative traumatic stimulation and preoperative pain, and intraoperative skin, muscle and nerve incisions. Pain impulses produced by bones; ②Inflammatory response caused by nerve injury and activation of ectopic neurons and trauma impulse after surgery. Therefore, the best method is to prevent the transmission of pain signals from tissue damage to wound healing, and minimize the influence of factors that help inhibit peripheral and central sensitization in the three stages of peripheral and central sensitization. Treatment is a suitable target for late analgesics. In addition, the surgical procedure, scale, duration, operation time, analgesic methods and

the nature of analgesic drugs before the tissue injury will also affect the degree of pain after the operation. Conduction of pain from the periphery to the center is a complex process and depends on the balance between excitatory and inhibitory systems. One or several stages of pain transmission can be blockaded to prevent peripheral and central hypersensitivity.

## 5 Conclusion

Preemptive analgesia is a balanced pain-relief. Using different analgesics and different methods of analgesia to block peripheral sensitization and central sensitization in different parts of the body can not only achieve good analgesic effects, but also reduce the side-effects of drugs and reduce the economic burden on patients.

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