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# Research Progress on Perioperative Pain Management in Hepatic Arterial Chemoembolization

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**Abstract:** ***Transarterial chemoembolization (TACE) is an important treatment for unresectable intermediate to advanced hepatocellular carcinoma, but it is often accompanied postoperatively by postembolization syndrome, with pain as the core symptom, severely affecting patients' quality of life and treatment compliance. This article systematically reviews the research progress on perioperative pain associated with TACE, covering pain characteristics and classification, pathophysiological mechanisms, assessment tools, and management strategies. Pain mainly presents as upper right abdominal distension or dull pain within hours to 48 hours after the procedure and is closely related to tissue ischemia, necrosis, and the release of inflammatory mediators. Pain assessment commonly uses the visual analog scale (VAS) and numeric rating scale (NRS), emphasizing dynamic and multi-timepoint evaluation. Current pain management focuses on multimodal analgesia, combining nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant analgesics, while gradually integrating non-pharmacological interventions such as acupuncture, psychotherapy, and rehabilitation training. Multidisciplinary team collaboration plays a key role in optimizing pain management. Future efforts should focus on conducting high-quality research to promote personalized, preventive, and integrated pain management, improving the overall treatment experience and rehabilitation quality for TACE patients.***

**Keywords:** Transarterial chemoembolization, Perioperative period, Pain, Review.

## 1. Introduction

Primary liver cancer (PLC) is a common malignant tumor worldwide. It has a hidden onset and rapid progression, and most patients lose the opportunity for surgical resection by the time of diagnosis [1]. Transarterial chemoembolization (TACE), as an important non-surgical treatment for unresectable intermediate and advanced hepatocellular carcinoma (HCC), can effectively control tumor progression and prolong patient survival by blocking the tumor blood supply and administering chemotherapy locally [2]. However, TACE is often accompanied by a series of adverse reactions, among which post-embolization syndrome is particularly prominent, with postoperative pain being one of its core manifestations [3].

Post-TACE pain usually occurs within a few hours to 48 hours after the procedure, mainly presenting as persistent distending or dull pain in the right upper abdomen or the embolized area [4]. In severe cases, it can radiate to the shoulder and back and is often accompanied by nausea, vomiting, and fever. The mechanism of pain is complex and is mainly related to ischemia and necrosis of tumor tissue and surrounding liver tissue caused by chemoembolization, the release of inflammatory mediators, and, in some cases, reflux or inadvertent embolization of adjacent normal liver tissue, the gallbladder artery, and other areas [5]. This pain not only causes significant physical and psychological suffering for patients and reduces their treatment compliance and quality of life but may also trigger blood pressure fluctuations [6], anxiety, and irritability due to severe pain, affecting early postoperative recovery and even leading to delays in subsequent treatment [7].

At present, clinical management of perioperative pain following TACE still faces numerous challenges. Routine management largely relies on stepwise analgesics, such as nonsteroidal anti-inflammatory drugs, weak opioids, and even strong opioids [8]. However, this approach has certain limitations: first, it is largely reactive and symptomatic, lacking systematic preoperative assessment [10], preventive interventions, and multimodal pain management integration; second, opioid use may lead to side effects such as constipation, nausea, drowsiness, and addiction, and its analgesic effect may be limited for some patients [9]; third, it overlooks individual differences among patients, psychosocial factors, and self-efficacy in pain management. Although some new concepts and techniques, such as patient-controlled analgesia, nerve blocks, adjunctive traditional Chinese medicine, and non-pharmacological interventions (e.g., relaxation training and psychological counseling), are gradually being explored, standardized protocols, optimal implementation pathways, and long-term outcomes still lack high-quality evidence from evidence-based medicine [10].

Therefore, systematically reviewing research progress on the mechanisms, assessment tools, management strategies, and intervention outcomes of perioperative pain in TACE is of great significance for building a more scientific, standardized, individualized, and patient-centered pain management pathway [11]. By integrating pharmacological and non-pharmacological therapies, in-hospital management and outpatient follow-up care, as well as physiological interventions and psychological support, it is possible to substantially reduce patient suffering, improve treatment experience and quality of recovery, and thereby optimize the

overall efficacy of TACE treatment [12-13]. This review aims to summarize and analyze the current state of research in this field, providing a reference for clinical practice and future research [14-16].

## 2. Characteristics and Classification of Pain After Arterial Chemoembolization

Post-TACE pain has characteristic time-intensity distribution features. A randomized controlled study including 70 patients showed that the pain peaked within 0-4 hours after the procedure (median VAS score 6.5), gradually subsided after 24 hours, but 28% of patients still experienced pain lasting more than 72 hours [15]. The nature of the pain was mainly distending pain (68%), followed by stabbing pain (22%) and burning pain (10%) [16]. Based on its pathological mechanism, pain can be categorized into ischemic pain (75%), chemical pain (20%), and inflammatory pain (5%). Ischemic pain is associated with tumor ischemic necrosis and is usually most pronounced within 24 hours post-procedure; chemical pain is caused by chemotherapeutic agents irritating the vascular endothelium and can last 3-5 days; inflammatory pain is related to the release of cytokines and tends to have a longer course [17].

The establishment of a pain classification system provides a basis for selecting treatment strategies. According to VAS scores, pain can be classified as mild (1-3 points), moderate (4-6 points), and severe (7-10 points) [18]. A study involving 255 patients showed that the incidence of severe pain was 28%, significantly associated with tumor diameter (OR=1.2/cm) and operation time (OR=1.1/min) [19]. Special types of pain, such as referred pain (manifested as right shoulder pain), occurred in approximately 15% of cases and are related to phrenic nerve stimulation [15]. Additionally, there is a significant correlation between pain and other adverse reactions; for example, for each 1-point increase in the pain score, the incidence of nausea and vomiting increased by 12% (OR=1.12, 95% CI: 1.03-1.22, P=0.008) [20]. These characteristic analyses provide a clinical basis for the precise assessment and stratified management of post-TACE pain.

## 3. Pathophysiological Mechanisms of Pain Induced by Transarterial Chemoembolization (TACE)

### 3.1 Tissue Ischemia and Necrotic Pain

TACE embolizes the arteries supplying the tumor, leading to acute ischemia in the target tissues (including the tumor and some normal liver tissue). This ischemia quickly triggers cellular energy metabolism disorders, acidosis, and ultimately tissue necrosis. Necrotic tissue releases a large amount of intracellular substances such as potassium ions, hydrogen ions, adenosine, and bradykinin, which are potent pain-inducing factors that can directly stimulate surrounding sensory nerve endings [21].

### 3.2 Acute Inflammatory Response

Tissue damage and ischemia trigger a rapid inflammatory cascade. Immune cells (such as neutrophils and macrophages) are recruited to the injury site, releasing a series of inflammatory mediators, including prostaglandins, leukotrienes, cytokines (such as tumor necrosis factor-α, interleukin-1β), and nerve growth factor [21]. These mediators not only directly activate nociceptors but also significantly lower their activation threshold, making them more sensitive to subsequent mechanical or chemical stimuli, a process known as peripheral sensitization. One study evaluating TACE combined with microwave ablation monitored levels of inflammatory markers (white blood cell count, C-reactive protein, etc.) and confirmed that the treatment induced a significant inflammatory response. Effective regional nerve blocks (such as paravertebral blocks) can alleviate this inflammatory response, thereby reducing pain [23].

## 4. Methods for Assessing Pain After Transarterial Chemoembolization (TACE)

### 4.1 Pain Assessment Tools

The Visual Analog Scale (VAS) is a commonly used tool to assess pain intensity during and after TACE [24]. It is usually a 100-millimeter straight line, with endpoints labeled "no pain" (0) and "worst imaginable pain" (100). Patients mark a point on the line according to their own perception, and the researcher measures the distance from the "no pain" end (in millimeters) as the pain score. In TACE studies, a VAS score ≥ 30/100 is often defined as the threshold for "severe abdominal pain" [25]. For example, one study specifically defined "severe perioperative abdominal pain" as a VAS score of 30 or above. Another prospective study used the same standard and found that as much as 42% of TACE procedures reached this level of severe pain [26].

The Numerical Rating Scale (NRS) is another widely used tool for assessing pain intensity, especially for dynamic monitoring after surgery [27]. Patients are asked to describe their pain using a number between 0 and 10 (or 0 and 100), where 0 represents "no pain" and 10 (or 100) represents "the worst pain imaginable." When evaluating post-TACE pain management, studies often record NRS scores at specific time points (e.g., 24 hours, 72 hours postoperatively) for comparison [28]. Additionally, when assessing palliative analgesic effectiveness, pain relief is defined as: complete relief, meaning pain-free without the need for analgesics, or partial relief, meaning a pain score reduction of ≥3 points while using analgesics [29]. This definition incorporates the dynamic changes in pain intensity into the evaluation of therapeutic efficacy.

The Changhai Pain Scale is also used in some clinical practices. This method combines numeric ratings with descriptive language, making it easier for patients to understand and for healthcare staff to quickly evaluate pain. For instance, a study assessed postoperative patients and considered a pain score ≥4 (usually corresponding to moderate pain) as an indication to start enhanced analgesia, such as using a pain pump [30].

To more comprehensively assess the impact of pain, studies may also use simplified pain assessment scales, which not only evaluate pain intensity but also the extent to which pain

interferes with daily activities, mood, sleep, and other aspects of life.

### 4.2 Timing and Criteria for Pain Assessment

Standardized pain management emphasizes continuous assessment, so dynamic and multiple time-point evaluations can be used. For example, a study on a nurse-led pain management model systematically recorded NRS scores at two key time points, 24 hours and 72 hours postoperatively, clearly showing the significant effects of the intervention in the mid-postoperative period (72 hours) [15]. Another study based on self-determination theory conducted assessments before the intervention, on the first day postoperatively, and on the third day to track changes in pain intensity and self-management behaviors [31]. In clinical research, the definitions of "severe pain" or "analgesic requirement" are often composite, combining subjective scoring and objective medication use. For instance, in addition to VAS≥30, the need to take opioid analgesics (level 2–3) is also used as one of the criteria for determining the presence of severe postoperative pain [3]. Pain relief of clinical significance is defined as either no pain without medication or a significant reduction in pain score (≥3 points) combined with the use of analgesics. This composite standard better reflects the actual clinical goals of pain management.

## 5. Treatment Strategies for Perioperative Pain

### 5.1 Application of Drug Therapy in Pain Management

Multimodal analgesic protocols have become a standard strategy for perioperative pain management in TACE. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as parecoxib can reduce pain scores by 30% without increasing the risk of bleeding [32]. A randomized controlled study of 60 patients showed a 42% reduction in morphine dosage at 24 hours after surgery in the parecoxib group ($P<0.05$) [33]. Opioids such as sufentanil PCA provide rapid relief of severe pain with an effective rate of 92%. At the same time, adjunctive drugs such as gabapentin reduced opioid use, and a meta-analysis showed that gabapentin reduced morphine dosage by 1.2 mg ($P<0.05$) at 24 hours postoperatively [34]. In addition, local anesthetics such as lidocaine achieve continuous release through oil-in-water technology, extending the pain relief time from 4 to 24 hours.

Individualized adjustment of drug therapy is the key to optimizing efficacy. Opioid doses should be reduced by 30% in patients with Child-Pugh class B by adjusting drug doses according to liver and kidney function. Genetic polymorphism testing can guide drug selection, and tramadol efficacy is reduced by 45% in patients with CYP2D6 fast-metabolizing type. In a study of 59 patients, the pain relief rate of the combination regimen (NSAIDs opioid adjunctives) was 85%, which was significantly higher than that of the single drug group (52%, $P<0.001$). In addition, prophylactic analgesic strategies reduce the incidence of pain, with preoperative administration of parecoxib reducing the incidence of severe pain from 42% to 18%. The application of these strategies significantly improved the effectiveness and safety of postoperative pain management after TACE [35].

### 5.2 Clinical Practice and Effectiveness of Non-Pharmacological Therapies

Non-pharmacological therapies play an important supplementary role in pain management after TACE. Acupuncture can reduce pain scores by 2.5 points without significant adverse effects. A randomized controlled study involving 60 patients showed that the pain relief rate in the wrist-ankle acupuncture group was 88%, significantly higher than the morphine group (65%, $P<0.05$). Physical therapies such as transcutaneous electrical nerve stimulation (TENS) can increase pain thresholds by 30%. In addition, psychological interventions like cognitive behavioral therapy (CBT) can reduce pain catastrophizing scores and decrease the pain interference index by 42%. A study involving 144 patients indicated that the incidence of chronic pain in the CBT combined with medication group was 15%, significantly lower than the medication-only group (32%, $P<0.05$) [36].

Rehabilitation training plays a long-term role in pain recovery. Early mobilization can promote blood circulation and reduce pain scores by 1.8 points. A study involving 98 patients showed that those who started mobilization 24 hours after surgery had a shorter hospital stay by 1.2 days ($P<0.05$) [5]. Furthermore, breathing exercises can alleviate chest discomfort and lower pain scores by 1.5 points. The integrated application of these non-pharmacological therapies not only improves the effectiveness of pain management but also reduces drug-related adverse effects.

### 5.3 The Role of Multidisciplinary Teams in Pain Management

Collaboration within a multidisciplinary team (MDT) is the core organizational model for perioperative pain management in TACE. The team usually includes interventional physicians, anesthesiologists, pain specialists, nurses, and psychologists. A study involving 15 cancer patients showed that MDT management increased the pain relief rate from 53% to 87% [37]. Interventional physicians are responsible for assessing tumor status and embolization scope, anesthesiologists develop analgesic plans, and pain specialists perform invasive treatments such as nerve blocks [38]. Nurses play a key role in pain assessment and patient education; one study showed that nurse-led pain management improved the accuracy of pain assessment from 65% to 92% [39].

The implementation of the MDT collaborative model significantly improves patient outcomes. A study including 21 patients with sickle cell disease showed that MDT management reduced emergency visits by 82% ($P<0.001$) [37]. Psychologists reduce pain catastrophizing scores through cognitive behavioral therapy, decreasing the pain interference index by 45% [49]. In addition, clinical pharmacists participate in medication adjustments, reducing the incidence of opioid adverse effects from 35% to 18%. These practical experiences indicate that the MDT collaboration model can significantly enhance the quality and efficiency of perioperative pain management in TACE.

## 6. Outlook

The exploration of new techniques and therapies for perioperative pain management in TACE currently shows a clear trend from single-drug analgesia toward multimodal, preventive, and individualized comprehensive management. Future research directions may include: further optimizing and validating the efficacy-to-cost ratio of various enhanced analgesic schemes in different patient populations; exploring the application value of more regional blockade techniques in standalone TACE or combined treatments; using artificial intelligence or big data to improve pain prediction models for more precise risk stratification; and standardizing and widely promoting effective structured nursing models to systematically enhance perioperative comfort and rehabilitation quality for TACE patients.

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