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The Effectiveness and Safety of Multimodal Pre-Emptive Analgesia in the Perioperative Period of Mid to Advanced Hepatocellular Carcinoma Undergoing TACE

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Abstract: *Objective*: To evaluate the analgesic effect and safety of hydromorphone hydrochloride in PCIA combined with flurbiprofen axetil and pre-emptive analgesia in patients with TACE treatment for hepatocellular carcinoma. *Methods*: Backward observation was made on 90 patients with advanced liver carcinoma who performed TACE treatment in the First Affiliated Hospital of Sun Yat-sen University from January 2022 to October 2023, dividing them into Group A (continuous pump injection of 6 mg hydromorphone + 50mg flurbiprofen ester as background injection for 2 ml/h, additional single injection of 3 ml/10min, 15 minutes before surgery) and Group B (intravenous injection of 50 mg flurbiprofen ester during the operation, additional injection of tramadol 100 mg intramuscular injection if necessary). Groups were compared and analyzed at different time points in surgery and post-operation time from pain level (NRS), side effects, inflammatory indexes (PCT, IL-6), satisfaction rate. *Result*: NRS scores at 5 time points, during operation, immediately post-surgery, 12, 24 hours post-operation, Group A were significantly lower than Group B (Group A during operation 3.0, immediate postoperation 3.0 to 24h 1.0; Group 4.0 to 24h 1.0, all $P > 0.05$). The rate of adverse reactions were comparable between the two groups (all $P > 0.05$). The amount of PCT (0.23 ng/ml vs 1.15 ng/ml) and IL-6 (54.49 pg/ml vs 233.49 pg/ml) decreased post-surgery in Group A compared to Group B, but were not statistically significant difference ($P = 0.424$/$P = 0.502$), and more patients in Group A were relieved to grade score of pain relief 4 or above (86.7% vs. 60%, $P = 0.001$). *Conclusions*: Pre-emptive analgesia treatment using PCIA of hydromorphone hydrochloride combined with flurbiprofen axetil has better analgesic effect than routine analgesic therapy in postoperative care of mid to advanced hepatocellular carcinoma TACE, has good safety, and is worth of further promotion and verifying.

Keywords: Multimodal analgesia; Patient-controlled intravenous analgesia; Pre-emptive analgesia; TACE

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1. Introduction

Transarterial chemoembolization (TACE) is one of the main treatment methods for mid and advanced liver carcinoma, which can also cure some early-stage liver carcinoma, and is often used as an adjuvant treatment after resection of primary liver carcinoma, which can effectively improve the survival rate of liver carcinoma patients [1]. However, more than 70% of patients will experience different degrees of pain after TACE [2], and such severe pain not only affects the therapeutic efficacy and reduces patient satisfaction but also leads to serious cardiovascular and cerebrovascular complications [3]. Effective perioperative pain control is a concern for patients and an important factor in improving the success rate of surgery and patient satisfaction. In 2022, China introduced the first special guideline, Expert Consensus on Perioperative Pain Management in Interventional Treatment of Hepatic Malignancies, but it did not provide the best way.

The mechanism of TACE induced pain involves several elements: chemotherapeutic agents and embolic agents irritate the endothelium, and embolisation results in ischaemic necrosis of the tumour, which leads to local inflammatory oedema and an increase in hepatic peritoneal tension [3].

Ischemic necrosis of the tumour tissue often results in the release of painful inflammatory mediators [4]. For moderate pain caused by TACE, the 2022 Expert Consensus on Perioperative Pain Management in Interventional Treatment of Malignant Liver Tumours suggests using opioids as needed [5]. Hydrochloride hydromorphone is a potent semi-synthetic derivative of morphine that selectively activates μ-receptors in the central nervous system and is superior to morphine in terms of physical and chemical properties and clinical analgesia [6]. However, TACE is often accompanied by pain caused by inflammatory mediators released due to tumour necrosis, such as prostaglandin E and bradykinin, and the anti-inflammatory effects of opioid drugs are relatively weak [4]. Therefore, the analgesic efficacy of these drugs alone remains suboptimal [7].

As a non-steroidal anti-inflammatory drug, flurbiprofen ester inhibits cyclooxygenase, blocks arachidonic acid metabolism, stabilises the kinin-kinin-kininase release system, inhibits the synthesis of prostaglandins that cause pain and inflammation, and blocks the transmission of pain signals from the injured site to the central nervous system, thereby exerting anti-inflammatory, analgesic, and antipyretic effects [8]. Therefore, hydromorphone combined with flurbiprofen ester possesses the dual analgesic advantages of reducing somatic pain and visceral pain and presents significant advantages in postoperative analgesia after TACE for hepatocellular carcinoma. Patient-controlled intravenous analgesia (PCIA) achieves on-demand analgesia by setting a background dose and allowing patients to control their analgesia. For patients with moderate to severe pain caused by TACE, multiple guidelines also recommend PCIA for perioperative analgesia throughout the entire process [5].

To this end, this study analyzed the efficacy and safety of a combined analgesic regimen of hydromorphone and flurbiprofen ester during PCIA patient-controlled intravenous analgesia in the special period before and after TACE surgery, aiming to provide ideas and practical experience for perioperative analgesia management of TACE.

2. Objects and methods

2.1. Research subjects

This study included 90 patients with advanced hepatocellular carcinoma admitted to the First Affiliated Hospital of Sun Yat-sen University.

The inclusion criteria included:

(1) Liver carcinoma patients diagnosed with a history of hepatitis or HBsAg- positive according to the 2019

edition of the National Health and Health Commission's Guidelines for the Diagnosis and Treatment of Primary Liver Cancer;

(2) Age between 18–80 years old;

(3) Child-Pugh liver function of class A or B;

(4) Laboratory tests must meet the following criteria:

(i) Peripheral blood leukocytes ≥ 1.5×10^9/L;

(ii) Platelets count ≥ 50×10^9/L;

(iii) Haemoglobin concentration ≥ 80 g/L;

(iv) Serum ALT and AST not exceeding twice the upper limit of normal;

(v) Serum creatinine not exceeding 1.5 times the upper limit of normal;

(vi) INR < 1.5 or prothrombin time not exceeding the upper limit of normal + 4s;

(vii) Albumin ≥ 30 g/L;

(viii) Total bilirubin ≤ 34 mmol/L.

Exclusion criteria:

(1) People with previous allergy to iodine;

(2) People with severe mental illness or psychological diseases;

(3) People taking analgesic drugs for a long period;

(4) Concurrent severe cardiopulmonary diseases;

(5) People with obvious fever or pain symptoms.

2.2. Research methods

2.2.1. Grouping and analgesic regimen

Using the random number table method, 90 patients were randomly divided into a multimodal analgesic group and a control group, with 45 patients in each group.

The analgesic regimen of the experimental group was as follows: hydromorphone hydrochloride 6 mg (2 ml: 2 mg, Hubei Yichang Renfu Pharmaceutical Co., Ltd.) and flurbiprofen ester 50 mg (5 ml: 50 mg, Beijing Taide Pharmaceuticals) were dissolved in saline until the total amount reached 100 ml and administered via PCIA. The drug dose for the PCIA pump was calculated based on 48 hours, and the pump was activated 15 minutes before the operation, with a background dose set at 2 ml/h, a single bolus dose of 3 ml, a lockout time of 10 minutes, and a maximum dose of 20 ml.

The analgesic regimen for the control group was as follows: when the patient experienced pain, 50mg of flurbiprofen ester was administered via intravenous infusion in 100ml of saline; if the analgesic effect was inadequate, an additional intramuscular injection of tramadol 0.1g (2ml: 0.1g, Granta GmbH, Germany) was administered.

Both groups of patients received prophylactic intravenous administration of 0.25 mg of palonosetron (5 ml: 0.25 mg, Hangzhou Jiuyuan Gene Engineering Co., Ltd.) before surgery. If significant nausea and vomiting discomfort recurred within 48 hours postoperatively, 10 mg of metoclopramide (10 mg/vial, Henan Runhong Pharmaceutical Co., Ltd.) was administered via intravenous push.

2.2.2. Programmatic pain education

Pain education is conducted on the day of admission, one day before surgery, and on the day of surgery. During the

education sessions, informational brochures are distributed, and various forms of instruction are used, including video presentations, demonstrations, and electronic educational devices, which last between 10 and 20 minutes. The educational content covers medical knowledge related to pain, multimodal pain management methods, pre-emptive pain management strategies, operation of patient-controlled intravenous analgesia pumps, and pain assessment methods.

2.2.3. TACE treatment

After local anesthesia with 2% lidocaine, both groups of patients underwent femoral artery puncture on the right side using the Selinger puncture method. After selectively inserting the catheter into the celiac trunk or superior mesenteric artery, selective angiography was performed. Based on the angiographic characteristics, microcatheter super-selective technology was used for precise infusion into the tumour-supplying arteries. Iodized oil (10 ml: containing 480 mg/ml iodine, Jiangsu Hengrui Medicine Co., Ltd.) and Pharmorubicin RD (10 mg/bottle, Wuxi Pfizer) were slowly injected. The infusion rate was adjusted based on the pharmacokinetic characteristics of the drugs. After blood flow slowed, a 40 mg suspension of Callisphere (100–300 μm, Jiangsu Hengrui Medicine Co., Ltd.) and Pharmorubicin RD (10 mg/bottle, Wuxi Pfizer Pharmaceutical Co., Ltd.) was injected for embolization.

During embolization, the procedure is performed based on the anatomical location of the tumour's blood supply vessels. After the embolization material has stabilized and settled, the catheter is withdrawn. The puncture site is compressed for 15 minutes to stop bleeding, then bandaged under pressure. After returning to the ward, the right hip joint is immobilized for 6–8 hours.

2.2.4. Observation indexes and methods

(a) Pain score

The Numerical Rating Scale (NRS) was used to assess variations in pain intensity at specific perioperative time points (intraoperative, immediate postoperative, and 1, 6, 12, and 24 hours postoperatively). The NRS scoring range was 0–10 points, with 0 points representing no pain, 1–3-point interval representing mild pain, 4–6-point interval representing moderate pain, and 7–10-point interval representing severe pain.

(b) Dosage of hydromorphone hydrochloride and rate of remedial analgesia

The dosage of hydromorphone hydrochloride and the corresponding remedial measures were recorded in detail for intraoperative and postoperative bursts of pain. If pain remains unrelieved, an intravenous bolus of 50 mg dexketoprofen in 100 mL saline solution or an intramuscular injection of 0.1 g tramadol was administered.

(c) Serum inflammatory factor

Fasting venous blood samples were collected from patients upon waking in the morning, both preoperatively and 24 hours postoperatively.

(d) Patient satisfaction score

Patient satisfaction was continuously monitored using a 5-point Likert scale: 5 as very satisfied, 4 as satisfied, 3 as average, 2 as dissatisfied, 1 as very dissatisfied.

(e) Occurrence of adverse reactions

Record adverse events within 24 hours after operation, primarily noting nausea and vomiting, dizziness, respiratory depression, skin pruritus, and urinary retention, among others. Tabulate the number of patients

experiencing the above adverse reactions.

2.2.5. Statistical analysis

Statistical analysis was performed using SPSS 25.0 software. The count data were expressed as constituent ratios; normally distributed measurements were expressed as mean ± standard deviation (SD); the t-test was used for inter-group comparisons, and one-way analysis of variance (ANOVA) was used for multi-group comparisons. Non-normally distributed measures were expressed as median (interquartile range), with the Mann-Whitney U test for comparisons between two groups and the Kruskal-Wallis H rank sum test for comparisons between multiple groups. In correlation studies, Spearman's correlation analysis was used. $\alpha = 0.05$ (two-tailed) was the significance level, and $P < 0.05$ was deemed statistically significant.

3. Results

3.1. General information

The study commenced by enrolling 160 patients with intermediate and advanced hepatocellular carcinoma admitted to the First Affiliated Hospital of Sun Yat-sen University. Following the exclusion criteria, 58 patients were excluded.

Among these, 17 patients had a history of long-term analgesic use; 11 patients experienced significant postoperative fever or pain; 2 patients were over 80 years of age; 7 patients had severe preoperative cardiopulmonary disease; 13 patients had incomplete records; and 8 patients had platelet counts < 50×10^9/L. A total of 12 patients in both groups were lost in the follow-up process. Ultimately, 90 patients were included in this study, with the inclusion and exclusion process detailed in **Figure 1**.

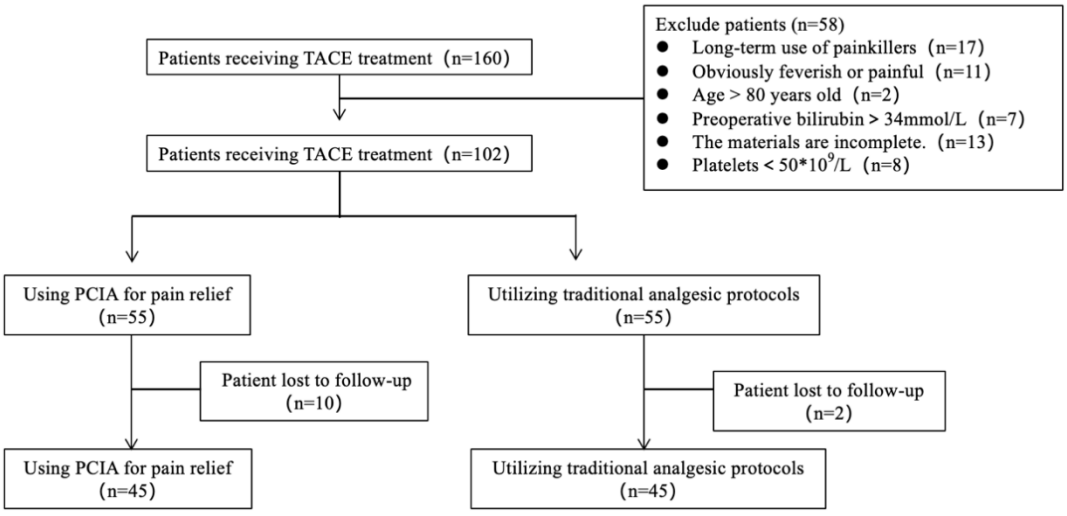

Figure 1. Patient admission and discharge process.

There was no statistically significant difference between the two groups in terms of gender, age, BMI, Child-Pugh classification, CNLC stage, prior TACE treatment history, or surgical duration ($P > 0.05$), as shown in **Table 1**.

Table 1. Clinical baseline characteristics of the two patient groups

Item	Experimental group (n=45)	Control group (n=45)	*P*-value
Gender			
Male	38	35	0.419
Female	7	10	
Age (years, mean ± SD)	54.64 ± 12.60	55.80 ± 11.94	0.609
BMI	22.12 ± 2.97	22.04 ± 3.16	0.899
Child-Pugh classification			
Grade A	45	40	0.205
Grade B	0	5	
CNLC stage			
Stage II	12	15	0.490
Stage III	33	30	
Tumour size			
< 5cm	33	29	0.362
≥ 5cm	12	16	
Tumour number			
Single	11	12	0.809
Multiple	34	33	
ECOG score			
0 point	10	8	0.598
1 point	35	37	
TACE treatment history			
Yes	7	11	0.292
No	38	34	
Duration of surgery(min)	65.00 (35.00–120.00)	60.0 (40.00–174.00)	0.551

3.2. Pain control status

There were significant differences in the NRS scores between the two groups at five time points: intraoperative, immediately postoperatively, and at 1 hour, 6 hours, and 24 hours postoperatively ($P < 0.05$), as shown in **Figure 2** and **Table 2**.

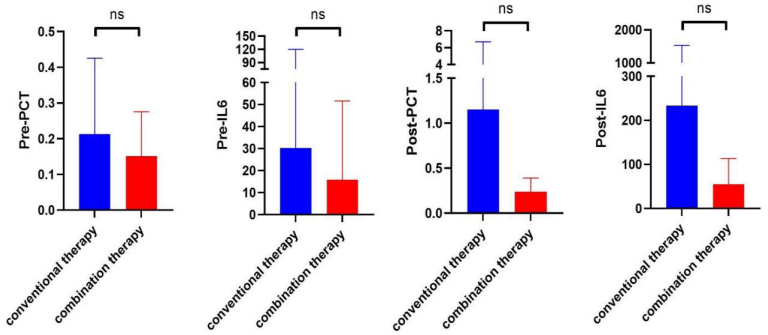

Figure 2. Comparison of NRS scores at different time points after TACE between the two patient groups.

Table 2. Comparison of NRS scores at different time points post-TACE between two patient groups

Group	Intraoperative	Immediately	1h after	6h after	12h after	24h postoperative
Experimental group (n=45)	3	3	4	3	2	1
Control group (n=45)	4	4	5	3	2	1
P-value	< 0.001	0.004	0.009	0.015	0.983	0.011

3.3. Comparison of preoperative and 24-hour postoperative serum inflammatory index levels between the two groups

There was no significant difference in the preoperative PCT and IL-6 levels between the two groups. Postoperative PCT (0.23 ng/ml vs. 1.15 ng/ml, P = 0.424) and IL-6 (54.49 pg/ml vs. 233.49 pg/ml, *P* = 0.502) levels of the patients in Group A were lower than those in Group B, with no statistically significant difference, as shown in **Figure 3**.

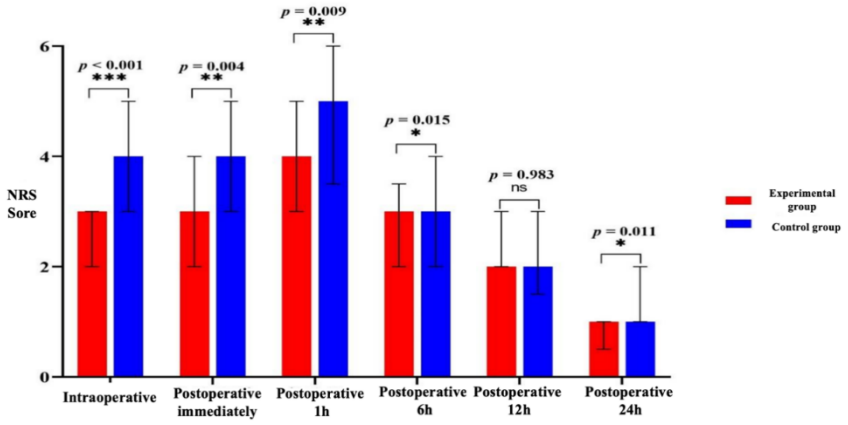

Figure 3. Comparison of preoperative PCT and IL-6 levels between the two groups of patients.

3.4. Adverse drug reactions

Common adverse reactions observed in patients during clinical application of hydromorphone include nausea, vomiting, dysuria, pruritus, and bradycardia. Analysis comparing adverse event incidence between the multimodal group and control group revealed no statistically significant difference in adverse reaction rates between the two groups ($P > 0.05$). See **Table 3** for details.

Table 3. Comparison of postoperative adverse reactions between the two groups of patients

Group	Nausea and vomiting	Dizziness	Respiratory depression	Pruritus	Dysuria
Experimental group (n = 45)	20	13	0	3	1
Control group (n = 45)	13	7	0	3	1
Chi-square value	2.344	2.314	0.000	0.000	0.000
P-value	0.126	0.128	1.000	1.000	1.000

3.5. Analgesic satisfaction scores

Analgesic satisfaction reflects the quality of perioperative pain control. At 48 hours postoperatively, patients in the multimodal analgesia group demonstrated significantly higher satisfaction with pain relief compared to the control group. Within the experimental group, 86.7% of patients reported satisfaction scores of 4 or above, whereas this figure stood at 60.0% in the control group. This difference was statistically significant ($P < 0.05$), as detailed in **Table 4**.

Table 4. Comparison of analgesic satisfaction scores between the two patient groups

Number of cases [n (%)]	1 point (Very poor)	2 points (Poor)	3 points (Fair)	4 points (Good)	5 points (Very good)
Experimental group	0 (0.0)	1 (2.2)	5 (11.1)	30 (66.7)	9 (20.0)
Control group	0 (0.0)	2 (4.4)	16 (35.6)	20 (51.1)	4 (8.9)

4. Discussion

China accounts for approximately 50% of global primary liver cancer cases, with an extremely high mortality rate, making it the second most common malignant tumor after lung cancer [9]. TACE involves injecting embolization agents and chemotherapy drugs into the hepatic artery to block the blood supply and kill tumour cells. It is currently recognized as the most effective non-surgical treatment for primary liver cancer, with nearly 100,000 TACE procedures performed annually in China [10]. While TACE treatment can slow tumour growth and prolong patient survival, it also induces adverse reactions and complications.

Postoperative pain is one of the common clinical symptoms following TACE. According to relevant studies, 75% of patients experience varying degrees of hepatic pain postoperatively, with 93% reporting severe pain [11]. Traditional analgesia relies on single drugs or monotherapy, yielding limited efficacy and often accompanied by significant adverse effects. Multimodal analgesia, however, combines analgesics with different mechanisms of action, employing a multi-pathway, multi-level, and multi-stage strategy. This approach has demonstrated significant efficacy in alleviating postoperative pain following TACE [12].

Hydrocodone, as a potent μ-opioid receptor agonist, exhibits a more rapid onset of action than morphine, delivers superior analgesia, offers greater safety, and is associated with fewer adverse reactions. Consequently, it has gained increasing application in patient-controlled intravenous analgesia (PCIA) [13]. However, high-dose hydromorphone may induce adverse reactions such as nausea, vomiting, and respiratory depression, and its analgesic efficacy remains inadequate in some patients [6]. This may be related to the release of pain-inducing inflammatory mediators from tumour tissue necrosis following TACE [4].

Flurbiprofen esters, a non-steroidal anti-inflammatory drug, effectively suppress acute pain by acting on tumour cells, surgical wounds, and vascular injury sites. They exert analgesic and anti-inflammatory effects by inhibiting cyclooxygenase activity, thereby reducing or blocking prostaglandin synthesis [14–18]. However, the analgesic effect of NSAIDs exhibits a ‘ceiling effect’, meaning that beyond a certain dose, further increases yield limited improvement in pain relief. When used alone, they typically alleviate only mild pain and often fail to adequately relieve moderate to severe pain in the early postoperative period. Consequently, combination with opioid analgesics is frequently required [19]. Research demonstrates that combined systemic administration of opioids and non-steroidal anti-inflammatory drugs yields superior postoperative analgesia compared to

monotherapy, whilst concurrently reducing the incidence of postoperative nausea, vomiting, and respiratory depression, thereby promoting patient recovery [20].

A retrospective study indicated that combining PCIA with flurbiprofen ester and hydromorphone yields superior analgesic effects in surgical patients [21]. The results of this study demonstrate that patients receiving combined hydromorphone and flurbiprofen ester via PCIA for perioperative analgesia during TACE exhibited lower pain scores than the control group during surgery, immediately postoperatively, and at 1, 2, and 24 hours postoperatively. No significant differences were observed in adverse reactions, suggesting that combined analgesic therapy based on PCIA demonstrates superior efficacy and safety in reducing perioperative pain during TACE compared with conventional monotherapy.

Once patients experience pain, they often develop a subjective desire to eliminate it urgently. During the period of waiting for medication to exert its analgesic effect, treatment comfort and satisfaction may diminish due to perceived excessive waiting times, excessive medication dosages, or excessive side effects. Consequently, this study employs the concept of pre-emptive analgesia within a multimodal pain management framework. This approach involves early intervention to inhibit central sensitisation before peripheral and central neural sensitisation occur, thereby reducing or eliminating nociceptive pain induced by injurious stimuli. Research indicates that pre-emptive analgesia yields favourable pain relief outcomes in patients undergoing uterine artery embolization, inhibits inflammatory mediators, and reduces both analgesic consumption and adverse drug reactions. Further studies indicate that administering analgesics before TACE treatment elevates the patient's analgesic threshold for TACE, effectively enhancing pain relief and comfort [22]. Consequently, the approach adopted in this study, initiating the analgesic pump 15 minutes preoperatively, adheres to the principles of pre-emptive analgesia, thereby reducing perioperative pain levels during TACE and improving patient satisfaction.

The severity of perioperative pain in patients undergoing TACE may be associated with inflammatory responses and inflammatory mediators [23,24]. Previous studies indicate that hyperalgesia and hypoalgesia induced by inflammatory responses and mediators are significant factors influencing pain intensity [24]. This study found no significant preoperative differences in PCT or IL-6 levels between the two groups. Postoperatively, PCT and IL-6 levels in Group A were lower than those in Group B, though the differences were not statistically significant, potentially due to the small sample size. This result aligns with the previously mentioned conclusion that tumour tissue necrosis following TACE leads to the release of pain-inflammatory mediators. It further suggests that combined analgesic methods based on PCIA can effectively reduce the degree of inflammatory response after TACE.

Additionally, we assessed the safety and patient experience of multimodal analgesia by monitoring perioperative adverse reactions during TACE and evaluating patients' pain relief satisfaction scores. Results indicated no statistically significant difference in adverse reaction incidence between the two groups, suggesting that the combined analgesic approach based on PCIA demonstrated comparable safety to conventional analgesic methods. The proportion of patients reporting satisfaction or higher in the experimental group was significantly higher than in the control group, indicating that multimodal analgesia provides patients with a better healthcare experience. This may enhance patient compliance in subsequent treatments.

5. Conclusion

The findings of this study suggest that, compared to traditional single-drug administration, PCIA-based combined

pre-emptive analgesia with hydromorphone hydrochloride (6 mg) and flurbiprofen ester (50 mg) significantly reduced postoperative pain intensity across all time points during the perioperative period of TACE treatment. This approach may mitigate postoperative inflammatory responses and markedly enhance patient satisfaction with perioperative analgesia, and does not increase adverse reactions, holding significant implications for perioperative pain management in TACE procedures. However, this study has limitations. Procedures were performed by the same medical team, and as the data originated from a single centre and were retrospective, generalisability may be constrained. Validation through larger prospective studies is warranted.

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Disclosure statement

The authors declare no conflict of interest.

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