

Impact of Perioperative Use of Parecoxib on Chronic Postsurgical Pain in Elderly Patients Undergoing Hepatectomy: A Prospective Randomized Controlled Study

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Research article

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Abstract

Background Chronic postsurgical pain (CPSP) in elderly patients negatively impacts recovery, quality of life, and physical functioning. This study aimed to test parecoxib's superiority versus placebo in combination with epidural anesthesia in preventing chronic post-hepatectomy pain in elderly patients.

Methods One hundred and five elderly patients undergoing hepatectomy were randomized to the parecoxib group or placebo group combined with epidural anesthesia. The primary outcome was the proportion of patients with CPSP at postoperative three months. The secondary outcomes included the Short-Form McGill Pain Questionnaire score in CPSP-positive responders, acute pain intensity, postoperative analgesic demand, inflammatory markers change, and postoperative complications within 28 days.

Results The parecoxib group provided a non-significant absolute 9.1% reduction in the rate of CPSP compared with the placebo group (35.3% vs. 44.4%, $P=0.34$). The average chronic pain verbal analog scale in the parecoxib group was lower than that in the placebo group (median (IQR) 2(1, 2) vs. 3 (2, 3), $P=0.04$). Significantly less moderate-to-severe acute pain at rest (4.3% vs. 17.3%, $P=0.04$) and with coughing (32.6% vs. 73.1%, $P<0.001$), less patient-controlled epidural analgesia (PCEA) consumption (197.4±43.6mL vs. 219.2±42.4mL, $P=0.01$) and less rescue analgesia (median (IQR) 0 (0, 0) vs. 1 (0, 2), $P<0.001$) were observed in parecoxib group. Furthermore, there was no between-group difference in inflammatory markers ($P>0.05$) and postoperative complications (11.8% vs.14.8%, $P=0.65$).

Conclusions Parecoxib reduced the prevalence of CPSP in elderly patients undergoing hepatectomy under epidural analgesia from 44.4% to 35.3% with no statistical significance. *Meanwhile*, significantly **alleviated** CPSP intensity and improved acute pain management were observed.

Trial Registration This study was retrospectively registered in the Chinese Clinical Trial Registry (URL: <http://www.chictr.org.cn/edit.aspx?pid=56961&htm=4>) on August 3, 2020 (ChiCTR-2000035198).

Background

In China, liver cancer is one of the most commonly diagnosed malignant tumors, mainly treated by surgical procedures. Though liver cancer incidence and mortality trend was decreasing significantly in recent years[1], China accounts for about half of the world's new cases each year [2]. Chronic postsurgical pain (CPSP), as a common long-existing postoperative complication, has been studied extensively in various surgeries[3] but rarely in open hepatectomy. However, the incidence of CPSP in living liver donors was reported as 31% at six months and 27% at one year postoperatively [4]. For patients undergoing liver transplantation, it was up to 70.5% at three months[5]. Approximately half of the elderly patients undergoing open hepatectomy complain of chronic pain during postoperative follow-up in our surgical center. For elderly patients, CPSP has no beneficial biologic significance and is believed to negatively impacts recovery, quality of life, and physical functioning[6]. Currently, preventing transformation from

acute pain into chronic pain is becoming an essential part of Enhanced Recovery After Surgery (ERAS)[7, 8].

The right subcostal incision is the most applicable method to open hepatectomy. With abdominal muscles and nerves transected, this incision brings many inflammatory mediators released and massive cellular reactions to severe tissue injury at surgical sites[9]. Persistent inflammatory changes enhance peripheral nociceptor sensitivity and further act on the central nervous system, which leads to peripheral sensitization and central sensitization. It is central sensitization that is thought to be the underlying mechanism for postoperative pain chronification. Nonsteroidal anti-inflammatory drugs (NSAIDs) are essential in perioperative multimodal analgesia strategy[8]. They have an inhibitory effect on cyclooxygenases, which play an anti-inflammatory role both in the spinal and peripheral nerve system[10]. As a representative, parecoxib acts selectively on cyclooxygenase-2 (COX-2), and it has been reported to be beneficial for acute postsurgical pain management[11]. Nevertheless, there is no substantial evidence to prove its function on CPSP. Therefore, we hypothesized that parecoxib could prevent CPSP by inhibiting the perioperative inflammatory reaction that facilitated central sensitization in elderly patients.

To test the hypothesis, we designed and conducted this prospective randomized controlled study enrolling elder patients undergoing hepatectomy in Zhongshan Hospital affiliated to Fudan University. Our institution has developed a routine practice of combined general-epidural anesthesia followed by patient-controlled epidural analgesia (PCEA) in liver surgery. We established a multimodal analgesia system by adding perioperative parecoxib to the routine practice. We set relatively strict criteria for entry and enrolled patients carefully to avoid possible adverse reactions due to parecoxib. Simultaneously, we evaluated other potential risk factors for CPSP after hepatectomy in our cohort.

Methods

2.1 Study Design

This study was a prospective, double-blind, random, placebo-controlled single-centered trial of perioperative analgesia to prevent CPSP in elderly patients undergoing hepatectomy. The trial's objective was to test the superiority of parecoxib's perioperative use compared to placebo in combination with epidural anesthesia in preventing CPSP at three months after surgery in the previously mentioned cohort.

2.2 Study Participants

All patients scheduling to undergo elective open hepatectomy for hepatocellular carcinoma, aged 65 to 80, with American Society of Anesthesiologists (ASA) physical status classification of I or II at Zhongshan Hospital, Fudan University, were considered eligible for this study. We excluded patients who underwent the previous hepatectomy, who gave a history of chronic pain, who were treated with radiation or chemotherapy, who were not suitable for epidural anesthesia, especially with coagulopathy, who had a history of psychology or mental illness. Given the potential adverse reactions of COX-2 inhibitors, patients

were excluded if they met one of the following conditions: 1. allergy to parecoxib; 2. active gastrointestinal bleeding or ulceration; 3. history of congestive heart failure or ischemic cardiac diseases; 4. Child-Pugh scores \geq 6 points or resection of more than three hepatic segments; 5. disease of peripheral arteries or cerebral vessels; 6. estimated glomerular filtration rate of less than 60 ml/min.

All participating patients gave written informed consent for this clinical trial, approved by the Ethics Committee of Zhongshan Hospital, Fudan University. A trial registration number (ChiCTR2000035198) was obtained from the Chinese Clinical Trial Registry.

2.3 Randomization and Blinding

By using a computer-generated randomization sequence, patients were recruited and allocated 1:1 to one of the following two treatment groups:

2.3.1. Parecoxib group: Parecoxib sodium of 40 mg diluted with normal saline to 4 ml was administrated intravenously immediately before initiating the surgical procedure and every 12 hours for three days.

2.3.2. Placebo group: Placebo was given on the same protocol with parecoxib sodium replaced by normal saline of 4 ml.

In this study, the patients, anesthesiologists, postoperative follow-up group, and data-processors were all blinded from the patients' grouping until all data were collected. Based on randomization, the pharmacist prepared the parecoxib sodium and placebo with identical appearance.

2.4 Study Procedures

2.4.1 Baseline psychological distress

All patients completed a questionnaire of the Hospital Anxiety and Depression Scale (HADS) the night before surgery.

2.4.2 Anesthesia implement

After the patient entered the operating room, we followed a standardized protocol to achieve general anesthesia combined with epidural block: 1) A central venous catheter was placed through the internal jugular vein to guide intraoperative fluid therapy. 2) An epidural catheter was properly placed at the T8-T9 interval, and the anesthesia plane was tested by 2% lidocaine of 3 ml. 3) General anesthesia was induced with fentanyl 3ug/kg, propofol plasma TCI, and rocuronium 0.6 mg/kg. 4) Intraoperative monitoring includes an electrocardiogram (lead II and lead V5), oxygen saturation, arterial blood pressure, central venous pressure, and end-tidal CO₂ partial pressure. 5) Anesthesia was maintained by 0.7MAC sevoflurane and continuous epidural anesthesia. Intraoperative fentanyl and muscle relaxants were administered on demand.

2.4.3 Multimodal analgesia

Patient-controlled epidural analgesia (PCEA) pump was applied to each patient after emergence from anesthesia, with the formulation of 0.12% ropivacaine and 2 ug/mL fentanyl. The infusion rate was 2 mL/h, bolus volume was 4 mL, and lock time was 10 min. Patients received parecoxib sodium or placebo intravenously immediately before the incision and once every 12 h till the 3rd day after surgery. Besides, non-NSAIDS rescue analgesia was available according to the surgeon's preference for postoperative breakthrough pain.

2.4.4 Index of Hematology

For each patient, venous blood was collected separately before surgery(D0)and on the day1(D1) and day 3(D3)after surgery to measure levels of the following items: leukocyte count (WBC), neutrophil count(N), lymphocyte count(L), prothrombin time(PT), activated partial thrombin time(APTT), highly sensitive C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6(IL-6), interleukin-8(IL-8) and interleukin-10 (IL-10).

2.4.5 Postoperative pain assessment and follow-up

Pain intensity was evaluated using a verbal analog scale (VAS) from 0 cm as no pain to 10 cm as the worst pain imaginable. Patients were assessed for pain intensity separately at rest and with coughing at 2, 4, 8, 24, 48, and 72 h post-surgery. The consuming volume and press times of the PCEA pump, the suspicious analgesic-associated adverse reactions, and any postoperative complications within 28 days were recorded.

Patients participating in the clinical trials were requested to complete a questionnaire via telephone three months after the surgery. They were questioned whether there was CPSP. If the answer was positive, states of CPSP was assessed using the Short-form McGill Pain Questionnaire (SF-MPQ).

2.5 Outcomes

The primary outcome was the proportion of patients with CPSP at three months after hepatectomy. Diagnostic criteria of CPSP were referring to the International Association For The Study Of Pain (IASP) definition[3]: 1) pain that develops or increases in intensity after surgical procedure and persists at least three months after surgery. 2) localized to the surgical field or projected to the innervation territory of a nerve situated around the surgical area. 3) a pain score on the VAS of greater than 1 cm. 4) pain due to pre-existing pain conditions or infections, malignancy was excluded. Secondary outcomes included the SF-MPQ score in CPSP-positive responders,acute pain intensity within 72 h after surgery, PCEA consumption, postoperative nausea and vomiting score at 24 h (0 = none, 10 = unbearable), perioperative change of hematology indexes and postoperative complications within 28 days.

2.6 Statistical Analysis

An observational data unpublished from patients undergoing liver surgery in our center revealed a CPSP prevalence of 48.6%. Based on an α of 5% and a power of 80%, a sample size of 44 patients per group was sufficient to detect a difference between the parecoxib group and the placebo group, given the

occurrence rate of 20% and 50%, respectively. To allow for 10% early withdrawals and loss to follow-up, 49 patients per group were enough. We finally included 105 patients in total. Based on a two-sided Fisher's Exact, the power for the primary outcome proportion of patients with CPSP was calculated as over 85%.

Database establishment and two-pass verification were performed using EpiData (version 3.1, EpiData Association, Denmark), and data analysis was conducted with IBM SPSS Statistics (version 22, IBM Corporation, USA). Data were reported as mean \pm SD, median (interquartile range), or number (percentage) of patients.

Data were compared using the Pearson chi-square test, t-test, or nonparametric test as appropriate. For repeated measurement, ANOVA was employed. Analysis of primary outcome was based on an intention-to-treat basis according to the previous randomization categories. To analyze the sensitivity of the results, the worst-case scenario and per-protocol analysis were both operated. The proportions of patients developing CPSP were compared using the Pearson chi-square test. No imputation was performed for missing data for the secondary outcomes.

To investigate other potential risk factors for CPSP after hepatectomy, logistic regression was performed by involving gender, ASA status, coexisting hypertension, the neutrophil-lymphocyte ratio (NLR) at baseline, and intervention. A type 1 error of 0.05 was used for all analyses.

Results

A total of 525 patients were screened, and 105 patients were recruited and assigned to receive intervention from November 2018 to July 2020 (Fig. 1). Ninety-five patients completed the follow-up at three months. Three patients lost to follow up due to death within three months. Seven patients withdrew from the study before the last assessment: one due to anaphylaxis, two due to failure epidural puncture, one due to recurrence, and three chose to stop. Data of all the ten patients above were included in the final analysis. Baseline patient characteristics were similar between the two groups (Table 1). Though patients in the parecoxib group have significantly different depression scores from those in the placebo group ($P = 0.03$), the clinical significance was inapparent. Because the cut-off of depression score in Hospital Anxiety and Depression Scale was 8 points, the depression status between-group was similar.

Table 1
Demographic, Baseline, and Morphometric Characteristics of Participants

Factor	Parecoxib Group (N = 51)	Placebo Group (N = 54)	P value
Demographic and baseline			
Age, y	69.9 ± 3.9	70.1 ± 4.2	0.79
Male, No. (%)	41(80.4)	38(70.4)	0.23
BMI, kg/m ²	23.6 ± 2.7	23.0 ± 3.1	0.33
ASA status, No. (%)			0.66
I	22(43.1)	21(38.9)	
II	29(56.9)	33(61.1)	
History of diabetes, No. (%)	3(5.9)	10(18.5)	0.05
History of hypertension, No. (%)	24(47.1)	26(48.1)	0.91
HADS- anxiety score, point	2(1to3)	2(0to5)	0.73
HADS- depression score, point	1(0to2)	0(0to1)	0.03 _a
Surgical characteristics			
Duration of surgery, h	2.5 ± 0.9	2.4 ± 1.1	0.43
Segment resected, No. (%)			0.07
1	25(49.0)	25(46.3)	
2	18(35.3)	11(20.4)	
3	8(15.7)	18(33.3)	
Pringle manerver duration, min	19.7 ± 12.4	18.9 ± 11.9	0.74
Intraoperative blood loss, ml	245.5 ± 188.8	229.1 ± 182.2	0.65
Intraoperative urine output, ml	277.5 ± 254.4	267.0 ± 233.9	0.83
Fluids volume (crystalloids, colloids), L	2.1 ± 0.6	1.9 ± 0.6	0.18

Data are reported as No. (%), means ± SD, or medians (IQR) as appropriate.

ASA, American Society of Anesthesiologists; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale.

_a Though patients in parecoxib group have significantly different depression scores from those in placebo group ($P = 0.03$), the clinical significance was inapparent. Because the cut-off of depression score in HADS was 8 points, the depression status between-group was similar.

Factor	Parecoxib Group (N = 51)	Placebo Group (N = 54)	P value
Intraoperative fentanyl infusion, ug/kg	3.7 ± 0.7	3.6 ± 0.7	0.44
Data are reported as No. (%), means ± SD, or medians (IQR) as appropriate.			
ASA, American Society of Anesthesiologists; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale.			
^a Though patients in parecoxib group have significantly different depression scores from those in placebo group ($P = 0.03$), the clinical significance was inapparent. Because the cut-off of depression score in HADS was 8 points, the depression status between-group was similar.			

3.1 Primary Outcome

The overall incidence of CPSP at three months was 40.0% (42 of 105) in the studied cohort. As stated in Table 2, perioperative multimodal analgesia with parecoxib did not lower the chance of developing CPSP at three months significantly compared with the placebo. The incidence was 35.3% in the parecoxib group and 44.4% in the placebo group, with RR(95%CI) for the parecoxib group of 0.794(0.493–1.279), $P = 0.34$. Results of sensitivity analyses, including both worst-case scenario and per-protocol analysis, remained no change.

Table 2
Primary Outcomes: Prevalence of CPSP at 3 Months

Primary Outcomes	Parecoxib group	Placebo group	RR (95% CI)	P value
CPSP at 3 mo, N (%)	18(35.3)	24(44.4)	0.794(0.493 ~ 1.279)	0.34
Worst-case scenario ^a	23(45.1)	24(44.4)	1.015(0.663 ~ 1.552)	0.95
Per-protocol analysis ^b	18(39.1)	24(49.0)	0.799(0.504 ~ 1.265)	0.33
CPSP, chronic postsurgical pain; CI, confidence interval; RR, relative risk.				
^a All patients lost to follow-up in the parecoxib group developed CPSP while all patients lost to follow-up in the placebo group didn't.				
^b Only patients who received allocated intervention and completed follow-up were included.				

3.2 Secondary Outcomes

Among the respondents who were experiencing CPSP at 3 months, there was no difference between parecoxib and placebo in the Pain Rating Index (median(IQR) 2(5) vs. 3(1, 6), $P = 0.32$) and the Present Pain Intensity (median(IQR) 1(1, 2) vs. 3(1, 2), $P = 0.44$; Table.3). However, VAS for average chronic pain in the parecoxib group was lower than that in the placebo group (median(IQR) 2(1, 2) vs. 3(2, 3), $P = 0.04$; Table.3). Moreover, 7.4%(4 of 54) patients developed moderate-to-severe average pain in the placebo group and none in the parecoxib group, though there was no significant difference with $P = 0.122$.

As represented in Table 3, postoperative pain intensity within 72 h in the parecoxib group was significantly higher than that in the placebo group, especially at 24, 48, and 72 h both at rest and with coughing. Meanwhile, patients in placebo group consumed more PCEA volume (219.2 ± 42.4 mL vs. 197.4 ± 43.6 mL, $P = 0.01$) and needed more rescue analgesia (median (IQR) 1 (1, 6) vs. 0 (0, 0), $P < 0.001$; Table 3). There were no differences between the two groups in postoperative analgesia-associated adverse reactions, length of stay in hospital after surgery, and postoperative complications within 28 days (Table 3.).

Table 3
Secondary Outcomes in Patients Receiving Parecoxib or Placebo Analgesia

Secondary Outcomes	Parecoxib Group	Placebo Group	P Value
SF-MPQ			
The Pain Rating Index	2(1to5)	3(1to6)	0.32
Sensory subscale	1(1to4)	2(1to3)	0.66
Affective subscale	0(0to1)	2(0to3)	0.08
Present pain intensity	1(1to2)	1(1to2)	0.44
Visual analog scale for average pain	2(1to2)	3(2to3)	0.04*
Moderate-to-severe acute pain at rest (VAS \geq 4 cm), N(%)	2(4.3)	9(17.3)	0.04*
Pain VAS score at rest, cm			
2 hours	0(0to0)	0(0to0)	0.88
4 hours	0(0to0)	0(0to0)	0.08
8 hours	0(0to0)	0(0to0)	0.93
24 hours	0(0to1)	1(0to2)	0.002*
48 hours	0(0to1)	1(0to2)	< 0.001*
72 hours	0(0to0)	1(0to2)	< 0.001*
Moderate- to-severe acute pain with coughing (VAS \geq 4 cm),N(%)	15(32.6)	38(73.1)	< 0.001*
Pain VAS score with coughing			
2 hours	0(0to0)	0(0to0)	0.72
4 hours	0(0to1)	1(0to1)	0.77
8 hours	1(0to2)	1(0to2)	0.98

Data are reported as No. (%), means \pm SD, or medians (IQR) as appropriate.

PCEA, patient controlled epidural analgesia; RR, relative risk; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale.

Asterisks for significance values.

Secondary Outcomes	Parecoxib Group	Placebo Group	P Value
24 hours	2(1to3)	3(2to4)	< 0.001*
48 hours	2(1to3)	4(2to5)	< 0.001*
72 hours	2(1to3)	3(2to5)	< 0.001*
Postoperative analgesia			
Total PCEA consumption within 72 h, mL	197.4 ± 43.6	219.2 ± 42.4	0.01*
Effective press rate, %	93.3 ± 12.8	93.9 ± 9.7	0.52
Rescue analgesia, time	0(0to0)	1(0to2)	< 0.001*
Nausea score at 24 hours (0 = none to 10 = unbearable)	0(0to5)	0(0to3)	0.46
Epidural adverse reactions, N(%)	12(24)	17(31.5)	0.40
Length of stay in hospital after surgery, days	7(7to10)	7(7to9)	0.56
Postoperative complications within 28 days, N(%)	6(11.8)	8(14.8)	0.65
RR (95% CI)	0.794(0.296–2.131)	-	
Pleural effusion, N(%)	1(2)	4(7.4)	0.36
Ascites, N(%)	1(2)	2(3.7)	1.00
Postoperative infection, N(%)	2(3.9)	1(1.9)	0.61
Cognitive dysfunction, N(%)	1(2)	0(0)	0.49
Urinary retention, N(%)	1(2)	0(0)	0.49
Acute pulmonary embolism, N(%)	0(0)	1(1.9)	1.00
Data are reported as No. (%), means ± SD, or medians (IQR) as appropriate.			
PCEA, patient controlled epidural analgesia; RR, relative risk; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale.			
Asterisks for significance values.			

Perioperative changes in inflammatory indexes were illustrated in Fig. 2. We could not find a significant influence of parecoxib than placebo on peripheral inflammatory parameters, including leukocyte count, NLR, hs-CRP, TNF- α , IL-1 β , IL-6, IL-8, and IL-10. Between-group differences of prothrombin time(P = 0.262) and activated partial thrombin time(P = 0.250) were not significant as well.

Post hoc analysis using logistic regression for gender, ASA status, coexisting hypertension, the NLR at baseline, and group intervention was set out in Table 4. In this model, ASA status and coexisting hypertension did not significantly affect the occurrence of CPSP at three months. However, the male and higher NLR at baseline were significantly related to developing CPSP in elderly patients undergoing primary hepatectomy.

Table 4
Logistic Regression Predicting Likelihood of CPSP at 3 Months

	B	SE	Wald	df	P value	Odds Ratio	95%CI
Parecoxib	0.429	0.450	0.907	1	0.341	1.535	0.635–3.711
Gender	-1.163	0.576	4.082	1	0.043*	0.313	0.101–0.966
ASA status	0.722	0.744	0.942	1	0.332	2.058	0.479–8.844
Hypertension	0.560	0.711	0.619	1	0.431	1.750	0.434–7.052
NLR at baseline	0.384	0.180	4.556	1	0.033*	1.469	1.032–2.090
Constant	-3.209	1.234	6.758	1	0.009*	0.040	
Reference for parecoxib was therapy with parecoxib; reference for gender was male; reference for ASA status was grade I.							
B,slope; CPSP, chronic postsurgical pain; CI, confidence interval; df, degrees of freedom; SE, standard error; NLR, neuro-lymphocyte ratio.							
Asterisks for significance values.							

Discussion

In our study, the overall prevalence of CPSP at three months after hepatectomy was 40%(42 of 105), and moderate-to-severe pain accounts for 3.8% (4 of 105). The result is consistent with a single-center observational study reporting a CPSP prevalence at three months of 50% in patients undergoing liver transplantation[5]. Meanwhile, with a similar incision to hepatectomy, open cholecystectomy has reported an incidence of CPSP varying from 3–50% [12]. The difference in CPSP incidence originated from differences in study design or selected study populations. Generally, CPSP is a substantial issue with clinical significance after open liver resection in elderly patients, though pain intensity is mild.

According to our results, parecoxib could not significantly reduce the prevalence of CPSP, despite an absolute decrease of 9.1%. This difference is far less than the 30% difference anticipated when estimating sample size. Results remained consistent in both the worst-case scenario and per-protocol analysis. Helmond et al. reached a similar conclusion in the patients after breast cancer surgery [13]. In contrast, Ling et al. 's study showed that parecoxib restrains chronic pain development significantly [14]. However, when interviewing those experiencing chronic pain by SF-MPQ, we observed a milder pain

intensity in the parecoxib group. Moreover, all four cases with moderate-to-severe average pain, ranging from 4 cm to 7 cm in VAS, occurred in the placebo group. Therefore, the study suggested that parecoxib does not significantly reduce the prevalence of chronic post-hepatectomy pain in elderly patients at three months but has a potential benefit of reducing chronic pain intensity. Perioperative use of parecoxib may be thereby helping to improve the quality of life in elderly patients with CPSP.

To understand how perioperative parecoxib took effect, we recorded a series of changes during the medication period. As confirmed by many studies[15], uncontrolled acute postoperative pain is a strong predictor of CPSP, possibly by provoking central sensitization[9]. In our study, the intensity of acute postoperative pain in two groups varied following similar trends: the pain intensity was trivial during the first eight postoperative hours, which gradually increased and reached the peak on the 3rd postoperative day. Some previous studies described consistent trajectories[16, 17]. We agree with the explanation that the excellent analgesia on the day of surgery is mainly due to sufficient epidural anesthesia. However, since the first day after surgery, the effects of epidural analgesia began to seem insufficient. Then the parecoxib's effect stood out: pain intensity tended to be significantly lower in the parecoxib group than in the placebo group. Meanwhile, a higher percentage of patients in the placebo group developed moderate-to-severe pain and needed more PCEA and rescue analgesia. Thus, the multimodal analgesia with parecoxib was proven to perform superior acute pain management in our study.

With analysis on a series of peripheral inflammatory indexes, we caught sight of the following facts:1) concentrations of hs-CRP and IL-6 increase gradually over time, the trend coincided with the postoperative pain intensity;2) peripheral leukocyte count, NLR, and IL-10 increase and reach the peak on the 1st postoperative day, then decrease on the 3rd day;3) there seems no connection between parecoxib and inflammatory changes in peripheral blood. Peng et al. found in aged rats that parecoxib inhibits hepatectomy-induced IL-1 β and TNF- α expression in the hippocampus through downregulation of the COX-2/PGE2 pathway[10]. Bjurstrom et al. reported that proinflammatory mediators in cerebrospinal fluid are associated with persistent postsurgical pain[18]. In clinical trials, due to technical limitations, real-time monitoring of central neuroinflammation is challenging to achieve. Though peripheral inflammatory markers are insensitive to reflect the real picture of neuroinflammation, our results suggest that1) level of systemic inflammation may indicate the intensity of acute pain;2) postoperative inflammatory and anti-inflammatory reactions are conducted simultaneously;3) the anti-inflammatory effect provided by parecoxib is insufficient to fight with the enormous postoperative inflammatory response that promotes central sensitization. Coincidentally, Turan et al. reported that even with glucocorticoids, the most potent anti-inflammatory drug, CPSP could not be prevented effectively[19]. Therefore, there may exist other mechanisms that dominate the development of central sensitization besides inflammation.

Surprisingly, we found that females had a reduced risk of developing CPSP in elder patients undergoing hepatectomy. The association between sex and pain has been widely studied. Sorge et al. revealed remarkably different pathways in male and female mice that determine pain hypersensitivity[20]. Hormone levels may play a role. We also found that a higher preoperative NLR was associated with the development of CPSP. Bugada et al. reported that NLR > 4 is correlated with persistent postsurgical pain

after inguinal hernia repair[21]. Other studies[22] have reported that psychologic factors, history of pre-existing chronic pain, and preoperative chemotherapy are also predictors. Therefore, CPSP may have been predetermined before surgery.

The application of NSAIDs in elderly patients has been controversial for the concerns of severe adverse reactions. NSAIDs-related adverse reactions include myocardial infarction, acute kidney failure, severe gastrointestinal ulceration, anaphylaxis, and coagulopathy. There was no significant difference between the two groups in postoperative complications and coagulation change in our study. Moreover, none of the above side effects were reported. One patient in parecoxib withdrew from the trial because of severe anaphylaxis on the first day after surgery. But parecoxib turned out to be innocent. However, given our small sample size, the power to evaluate those side effects is limited. Thus, the safety of parecoxib use in elderly patients remains further verification.

Our study has several limitations. It is a single-center RCT based on small sample size. The lack of statistical significance might result from low statistical power due to the small sample size. In consideration of potential adverse reactions associated with COX-2 inhibitors, we used stringent inclusion criteria. It inevitably reduced the sample size and affected the generalisability of our results. Our study's sample size was smaller than that in Kehlet's study[19] but similar to Anwar's[23]. However, few patients were lost to follow-up after receiving the assigned intervention, and sensitivity analysis showed that the final results were not affected by the lost cases. Similarly, we evaluated CPSP with SF-MPQ instead of using an objective clinical diagnosis. Investigation on the nature of chronic pain might be limited. In the future, multi-centered RCT for objective assessment with larger sample sizes should be conducted to seek better perioperative analgesia strategy for preventing chronic postsurgical pain in elderly patients.

Conclusions

In conclusion, parecoxib reduced the prevalence of CPSP in elderly patients undergoing hepatectomy under epidural analgesia from 44.4% to 35.3% with no statistical significance. Besides, parecoxib has a potential effect on reducing the CPSP intensity and optimizing postoperative acute pain management. Prudent but individualized use of parecoxib in those relatively healthy elder patients undergoing liver resection is recommended.

Abbreviations

CPSP: chronic postsurgical pain

PCEA: patient-controlled epidural analgesia

NSAIDs: nonsteroidal anti-inflammatory drugs

COX-2: cyclooxygenase-2

ASA: American Society of Anesthesiologists

HADS: Hospital Anxiety and Depression Scale

WBC: leukocyte count

N: neutrophil count

L: lymphocyte count

NLR: neutron-lymphocyte ratio

PT: prothrombin time

APTT: activated partial thrombin time

hs-CRP: highly sensitive C-reactive protein

TNF- α : tumor necrosis factor- α

IL-1 β : interleukin-1 β

IL-6: interleukin-6

IL-8: interleukin-8

IL-10: interleukin-10

VAS: verbal analog scale

SF-MPQ: Short-form McGill Pain Questionnaire

IASP: International Association For The Study Of Pain

IQR: interquartile range

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Zhongshan Hospital, Fudan University (Ethics approval number: B2018-185). All participating patients gave written informed consent for this clinical trial, approved by the Ethics Committee of Zhongshan Hospital, Fudan University.

Consent for publication Not applicable.

Availability of data and materials The datasets generated during the current study are available in the RESMAN repository, [<http://www.medresman.org>]

Competing interests The authors declare that they have no competing interests.

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Authors' contributions XDG and SJG were responsible for designed and facilitated the study. XDG, YP, and DFJ were responsible for the collection and assembly of data. XDG, YP, YW and DFJ were responsible for data analysis and interpretation. XDG wrote the first draft of the manuscript, which was revised by SJG. All authors discussed the results and commented on the manuscript.

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Tables

Table 1 Demographic, Baseline, and Morphometric Characteristics of Participants

Factor	Parecoxib Group (N = 51)	Placebo Group (N= 54)	P value
Demographic and baseline			
Age, y	69.9±3.9	70.1±4.2	0.79
Male, No. (%)	41(80.4)	38(70.4)	0.23
BMI, kg/m ²	23.6±2.7	23.0±3.1	0.33
ASA status, No. (%)			0.66
I	22(43.1)	21(38.9)	
II	29(56.9)	33(61.1)	
History of diabetes, No. (%)	3(5.9)	10(18.5)	0.05
History of hypertension, No. (%)	24(47.1)	26(48.1)	0.91
HADS- anxiety score, point	2(1to3)	2(0to5)	0.73
HADS- depression score, point	1(0to2)	0(0to1)	0.03 _a
Surgical characteristics			
Duration of surgery, h	2.5±0.9	2.4±1.1	0.43
Segment resected, No. (%)			0.07
1	25(49.0)	25(46.3)	
2	18(35.3)	11(20.4)	
3	8(15.7)	18(33.3)	
Pringle manerver duration, min	19.7±12.4	18.9±11.9	0.74
Intraoperative blood loss, ml	245.5±188.8	229.1±182.2	0.65
Intraoperative urine output, ml	277.5±254.4	267.0±233.9	0.83
Fluids volume (crystalloids, colloids), L	2.1±0.6	1.9±0.6	0.18
Intraoperative fentanyl infusion, ug/kg	3.7±0.7	3.6±0.7	0.44

Data are reported as No. (%), means ± SD, or medians (IQR) as appropriate.

ASA, American Society of Anesthesiologists; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale.

^aThough patients in parecoxib group have significantly different depression scores from those in placebo group ($P=0.03$), the clinical significance was inapparent. Because the cut-off of depression score in HADS was 8 points, the depression status between-group was similar.

Table 2 Primary Outcomes: Prevalence of CPSP at 3 Months

Primary Outcomes	Parecoxib group	Placebo group	RR (95% CI)	<i>P</i> value
CPSP at 3 mo, N (%)	18(35.3)	24(44.4)	0.794(0.493~1.279)	0.34
Worst-case scenario ^a	23(45.1)	24(44.4)	1.015(0.663~1.552)	0.95
Per-protocol analysis ^b	18(39.1)	24(49.0)	0.799(0.504~1.265)	0.33

CPSP, chronic postsurgical pain; CI, confidence interval; RR, relative risk.

^aAll patients lost to follow-up in the parecoxib group developed CPSP while all patients lost to follow-up in the placebo group didn't.

^bOnly patients who received allocated intervention and completed follow-up were included.

Table 3 Secondary Outcomes in Patients Receiving Parecoxib or Placebo Analgesia

Secondary Outcomes	Parecoxib Group	Placebo Group	P Value
SF-MPQ			
The Pain Rating Index	2(1to5)	3(1to6)	0.32
Sensory subscale	1(1to4)	2(1to3)	0.66
Affective subscale	0(0to1)	2(0to3)	0.08
Present pain intensity	1(1to2)	1(1to2)	0.44
Visual analog scale for average pain	2(1to2)	3(2to3)	0.04*
Moderate-to-severe acute pain at rest (VAS \geq 4 cm), N(%)	2(4.3)	9(17.3)	0.04*
Pain VAS score at rest, cm			
2 hours	0(0to0)	0(0to0)	0.88
4 hours	0(0to0)	0(0to0)	0.08
8 hours	0(0to0)	0(0to0)	0.93
24 hours	0(0to1)	1(0to2)	0.002*
48 hours	0(0to1)	1(0to2)	<0.001*
72 hours	0(0to0)	1(0to2)	<0.001*
Moderate- to-severe acute pain with coughing (VAS \geq 4 cm) N(%)	15(32.6)	38(73.1)	<0.001*
Pain VAS score with coughing			
2 hours	0(0to0)	0(0to0)	0.72
4 hours	0(0to1)	1(0to1)	0.77
8 hours	1(0to2)	1(0to2)	0.98
24 hours	2(1to3)	3(2to4)	<0.001*
48 hours	2(1to3)	4(2to5)	<0.001*
72 hours	2(1to3)	3(2to5)	<0.001*
Postoperative analgesia			
Total PCEA consumption within 72 h, mL	197.4 \pm 43.6	219.2 \pm 42.4	0.01*
Effective press rate, %	93.3 \pm 12.8	93.9 \pm 9.7	0.52

Rescue analgesia, time	0(0to0)	1(0to2)	<0.001*
Nausea score at 24 hours (0=none to 10=unbearable)	0(0to5)	0(0to3)	0.46
Epidural adverse reactions, N(%)	12(24)	17(31.5)	0.40
Length of stay in hospital after surgery, days	7(7to10)	7(7to9)	0.56
Postoperative complications within 28 days, N(%)	6(11.8)	8(14.8)	0.65
RR (95% CI)	0.794(0.296-2.131)	-	
Pleural effusion, N(%)	1(2)	4(7.4)	0.36
Ascites, N(%)	1(2)	2(3.7)	1.00
Postoperative infection, N(%)	2(3.9)	1(1.9)	0.61
Cognitive dysfunction, N(%)	1(2)	0(0)	0.49
Urinary retention, N(%)	1(2)	0(0)	0.49
Acute pulmonary embolism, N(%)	0(0)	1(1.9)	1.00

Data are reported as No. (%), means \pm SD, or medians (IQR) as appropriate.

PCEA, patient controlled epidural analgesia; RR, relative risk; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale.

Asterisks for significance values.

Table 4 Logistic Regression Predicting Likelihood of CPSP at 3 Months

	B	SE	Wald	df	P value	Odds Ratio	95%CI
Parecoxib	0.429	0.450	0.907	1	0.341	1.535	0.635-3.711
Gender	-1.163	0.576	4.082	1	0.043*	0.313	0.101-0.966
ASA status	0.722	0.744	0.942	1	0.332	2.058	0.479-8.844
Hypertension	0.560	0.711	0.619	1	0.431	1.750	0.434-7.052
NLR at baseline	0.384	0.180	4.556	1	0.033*	1.469	1.032-2.090
Constant	-3.209	1.234	6.758	1	0.009*	0.040	

Reference for parecoxib was therapy with parecoxib; reference for gender was male; reference for ASA status was grade I.

B,slope; CPSP, chronic postsurgical pain; CI, confidence interval; df, degrees of freedom; SE, standard error; NLR, neuro-lymphocyte ratio.

Asterisks for significance values.

Figures

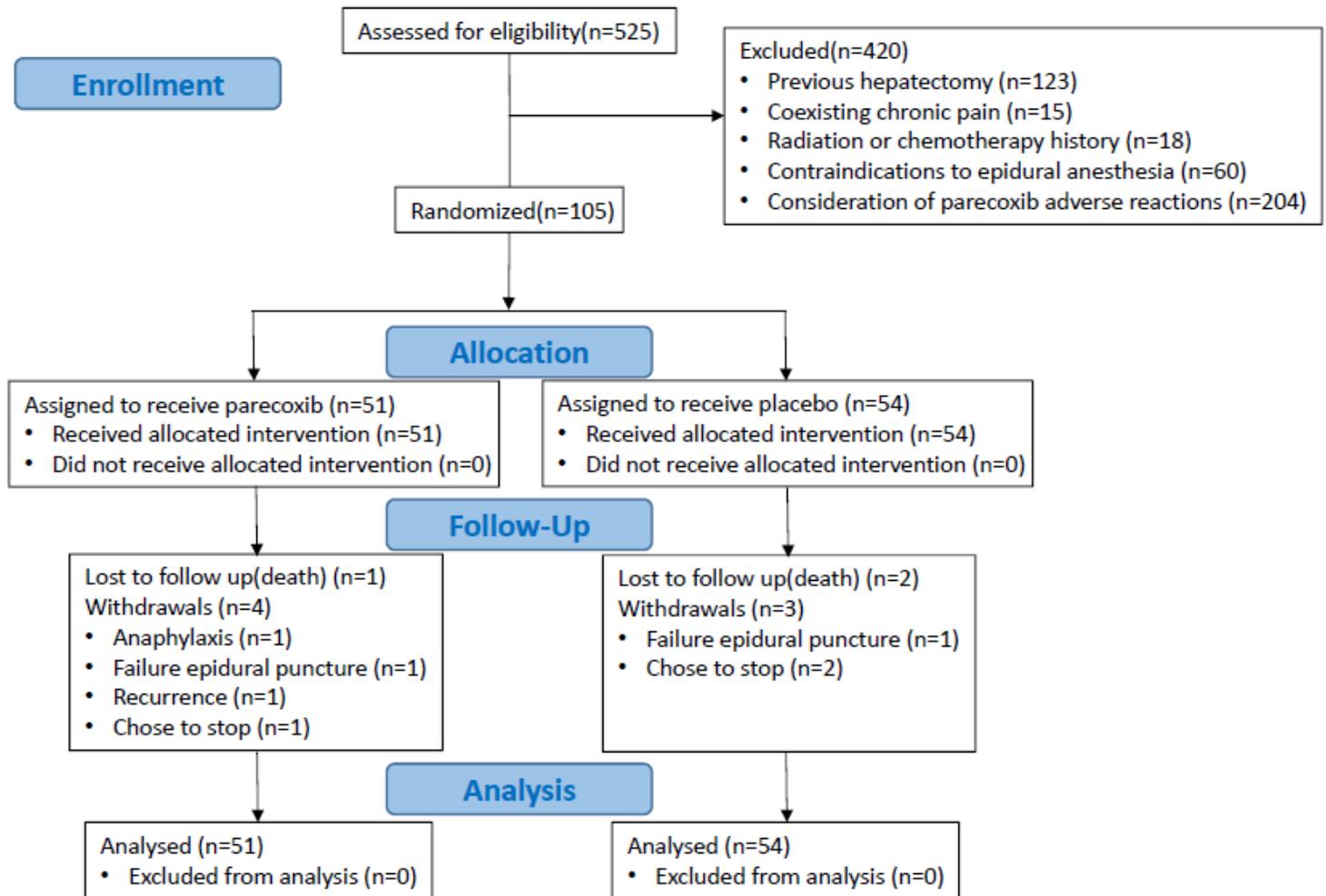


Figure 1

Flow chart

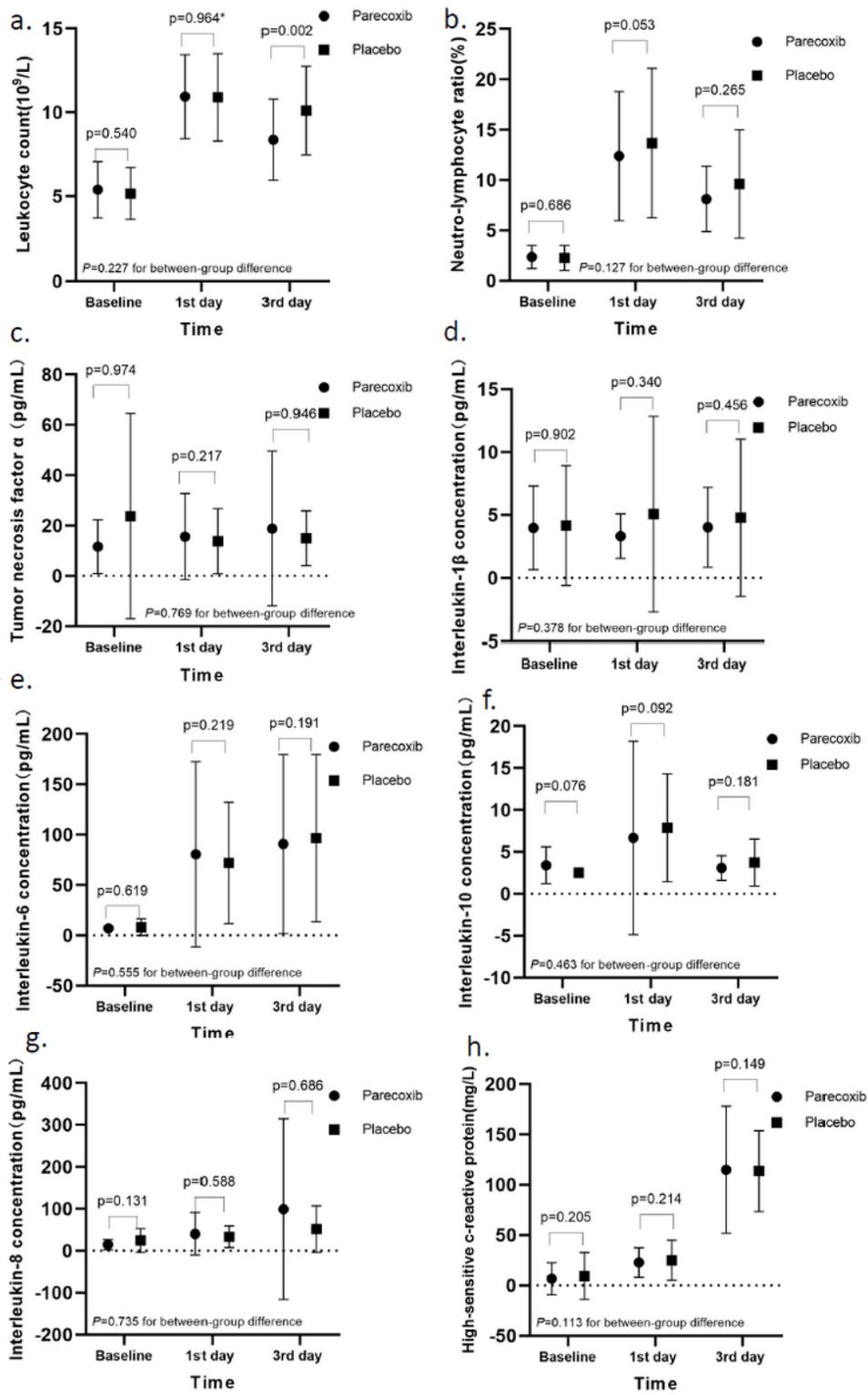


Figure 2

Perioperative change of inflammatory indexes.(a)demonstrates the leukocyte count change over time; (b) demonstrates the neutro-lymphocyte ratio change over time; (c) demonstrates the tumor necrosis factor-α change over time; (d) demonstrates the interleukin-1β change over time; (e) demonstrates the interleukin-6 change over time; (f) demonstrates the interleukin-10 change over time; (g) demonstrates the interleukin-8 change over time; (h) demonstrates the highly sensitive C-reactive protein change over time.

Spot or square for mean of the index. Length of bars for standard deviation. P values of inter-group comparisons at each timepoint were provided above bars. P values with asterisk were calculated with independent t-test. Unsigned P values with Mann-Whitney U test. P values for between-group difference was calculated with repeated measures ANOVA.

Supplementary Files

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