Routine use of intravenous acetaminophen safely enhances pain control after minimally invasive hepatectomies: a retrospective cohort study

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Abstract

Background Effective postoperative pain management is crucial after minimally invasive hepatectomy (MIH) to promote recovery, and multimodal analgesia strategies are used to reduce opioid requirements and improve outcomes. Acetaminophen is commonly included as part of multimodal therapies for postoperative pain management. However, the safety and efficacy of acetaminophen for postoperative analgesia in MIH remains unestablished due to its hepatic metabolism. This study aimed to evaluate the safety and efficacy of routine intravenous acetaminophen administration following MIH.

Methods The data of consecutive 50 patients who had undergone MIH were retrospectively analyzed. Regarding postoperative analgesia, patients were allocated to either the opioid-alone cohort (Cohort O) or opioid with routine intravenous acetaminophen cohort (Cohort A). Analgesic efficacy was evaluated using the numerical rating scale (NRS) over the first 2 postoperative days. The sum of opioid rescue doses and frequency of postoperative nausea and vomiting (PONV) were assessed. Analgesic safety was determined by monitoring prolonged elevated transaminase levels.

Results Postoperatively, no significant differences in the hepatic and renal functions and systemic inflammatory markers were observed between the two cohorts. On both postoperative day 1 and day 2, Cohort A showed significantly lower NRS scores than Cohort O. Notably, almost all patients in Cohort A did not require any rescue opioid doses, resulting in a significantly reduced median rescue dose (6 versus 0 doses, $p = 0.0017$). Even when opioid doses were reduced due to PONV, Cohort A continued to exhibit significantly lower NRS scores.

Conclusions Multimodal analgesia comprising routine intravenous acetaminophen administration could be safe and effective after minimally invasive hepatectomy, without adverse effects regarding hepatic function.

Keywords Acetaminophen, Analgesics, Opioid, Postoperative nausea and vomiting, Minimally invasive hepatectomy

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Background

Liver resection is technically challenging due to the liver's complex anatomy and rich blood supply [1]. Effective perioperative management, such as Enhanced Recovery After Surgery (ERAS) protocols is essential for improving surgical outcomes and reducing postoperative complications [2, 3]. Multimodal analgesia, including epidural anesthesia, intravenous opioids (such as fentanyl), peripheral nerve blocks (PNBs), non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen, is widely recognized for its effectiveness in managing postoperative pain following gastrointestinal surgery [4, 5].

Epidural anesthesia is effective; however, it carries the risk of complications, such as hemorrhage and epidural hematoma, particularly in patients who develop post-hepatectomy coagulopathies [6–8]. Opioids are effective for pain relief; nonetheless, they are associated with an increased risk of adverse effects, including constipation, sedation, and postoperative nausea and vomiting (PONV) [9]. PONV negatively affects the postoperative quality of life and may delay mobilization, resulting in a prolonged hospital stay [10].

Despite concerns regarding hepatotoxicity, acetaminophen administration as postoperative analgesia following an open hepatectomy has been shown to be safe [11, 12]. Minimally invasive liver resection (MIH) has evolved significantly in recent years, with improved surgical techniques and outcomes [13]. MIH is increasingly adopted as a standard approach due to its advantages in reducing surgical trauma and accelerating recovery. However, in MIH, the effects of decreased hepatic blood flow due to pneumoperitoneum pressure and patient positioning on drug metabolism have not been fully elucidated, and the safety and efficacy of acetaminophen administration post-MIH remains incompletely established. Moreover, few studies have objectively assessed an improvement in postoperative pain management with acetaminophen administration [14, 15]. We have hypothesized that the routine intravenous administration of acetaminophen provides effective postoperative analgesia, reduces the need for opioids, and minimizes the incidence of PONV in patients undergoing MIHs. Thus, in this study, we aimed to assess the safety and effectiveness of multimodal analgesia comprising the routine intravenous administration of acetaminophen in the postoperative pain management of MIH.

Materials and methods

Ethical considerations

This study has been approved by the Ethics Committee (EC) of Yamaguchi University Hospital, with the EC approval number: 2024-020. Moreover, this study has been conducted in accordance with the principles of the World Medical Association Declaration of Helsinki involving human patients (as revised in Brazil 2013). Written informed consent was obtained from the patients for the collection of their samples and publication of their de-identified data and images.
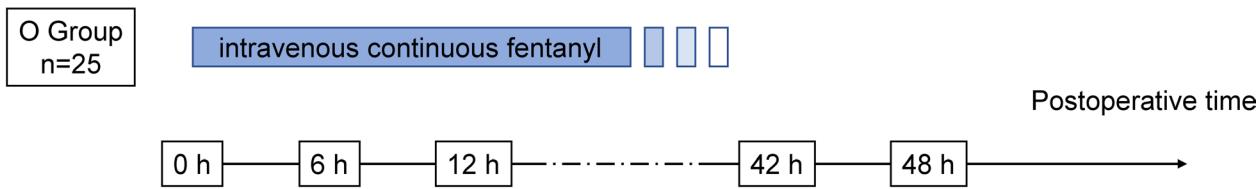
Patients and methods

In this retrospective single-center cohort study, 50 consecutive patients who had undergone MIHs between October 2021 and October 2022 were enrolled into the study; and their data were collected and analyzed. Anesthesia was managed with continuous intravenous remifentanil, fentanyl boluses, and sevoflurane inhalation. Nitrogen gas and epidural anesthesia were not administered. Some patients received PNBs during anesthetic management. The indication for PNBs was determined by the anesthesiologist based on clinical judgment, and transversus abdominis plane and rectus sheath blocks were performed under ultrasound guidance either before or immediately after surgery. A total of 40 mL of 0.25% levobupivacaine was administered as standard practice. All patients were managed with continuous intravenous fentanyl via intravenous patient-controlled analgesia (iv-PCA). Dosages and rates had been calibrated by the anesthesiologist, according to the age and weight of each patient, with an initial rate of 0.3–0.5 µg/kg/h, bolus dose of 10–20 µg/dose, and total dose of 1000–2000 µg. Rescue opioid doses were administered by patients themselves using iv-PCA when they experienced pain.

The patients were divided into two cohorts: Cohort O (opioids-alone, without the routine acetaminophen) and Cohort A (with the regular administration of acetaminophen). In Cohort A, acetaminophen was administered every 6 h until 48 h postoperatively, according to the manufacturer's protocol (body weight [BW] ≥ 50 kg: 1000 mg/dose; BW < 50 kg: 15 mg/kg/dose). These cohorts represent consecutive patients treated during distinct historical periods: Cohort O includes patients treated between October 2021 and March 2022, while Cohort A includes those treated between April 2022 and October 2022 (Fig. 1). In Cohort O, four patients received intravenous acetaminophen, but it was administered once or twice within 48 h postoperatively, not as routine dosing. Oral administration of acetaminophen or NSAIDs was initiated after 48 h postoperatively and was therefore excluded from the analysis.

Postoperative pain was evaluated for 2 days postoperatively, using a Numerical Rating Scale (NRS) at rest and during movement. NRS scores were recorded in the medical chart by the nurses and occupational therapists, who were blinded to the study protocol. The results were compared with the worst values of the day, evaluated at each visit. Furthermore, the total postoperative fentanyl dose and number of rescue doses were assessed. The frequency of PONV and sum of the antiemetic agent doses

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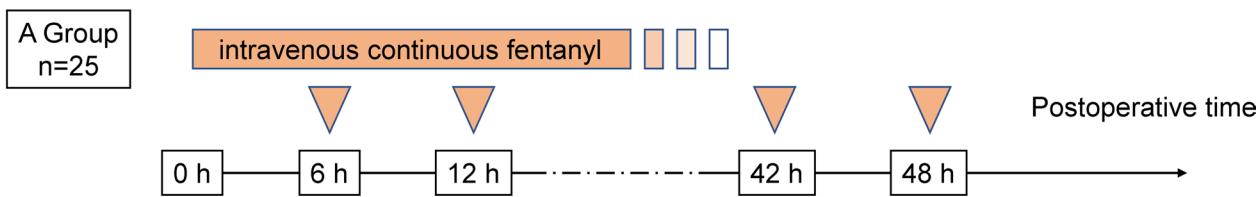
Fig. 1 Study design is depicted. Data of the study patients from the period of October 2021 to October 2022 have been included. The patients have been either assigned to the opioid-alone cohort (Cohort O, *n* = 25) or opioid with routine intravenous acetaminophen administration cohort (Cohort A, *n* = 25) for postoperative analgesia. Both cohorts have received continuous intravenous fentanyl. Cohort A has received intravenous acetaminophen every 6 h, until 48 h postoperatively, according to the manufacturer's protocol. Abbreviation: BW, body weight

were evaluated for safety and adverse effects. Hepatic function was monitored using serum laboratory examinations on the first, third, fifth, and seventh postoperative days. We measured aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (T.Bil), and prothrombin time (PT) as indicators of liver function. Acetaminophen-induced hepatotoxicity was considered absent if no abnormal elevations were observed in Cohort A compared to Cohort O.

Data were extracted independently by several researchers, and any discrepancies were resolved through discussion to ensure accuracy. A comprehensive electronic medical record system was used, and all data were thoroughly verified. There were no missing values among the variables included in the analysis; thus, no imputation or special handling was necessary.

Statistical analyses

The clinicopathological factors of Cohorts O and A were compared. Continuous and categorical variables in the clinicopathological factors were expressed as median values (with range) and frequencies, respectively. Differences in clinicopathological findings between the two groups were analyzed using the Mann–Whitney U test for continuous variables and chi-squared test for categorical variables; while perioperative liver function, renal function, and systemic inflammatory markers tests were compared applying the Benjamini and Hochberg method as multiple comparisons. Furthermore, univariate and multivariate analyses were performed using the

logistic regression model. The cut-off value for the intraoperative fentanyl dose was determined using a receiver operating characteristic curve analysis. Patients who had undergone PNBs were further divided into sub-cohorts. Regarding these sub-cohort analyses, the NRS, total postoperative fentanyl doses, and number of rescue doses were compared between Cohorts O and A. Statistical analyses were performed using JMP 15 software (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$.

Results

Clinical and surgical factors

This study included 50 patients who were divided into two cohorts: Cohort A ($n = 25$) and Cohort O ($n = 25$) (Table 1). Statistically significant differences were not observed between the two cohorts regarding the clinical features, including diseases and preoperative hepatic and renal functions. Ten and seven patients in Cohorts O and A, respectively, underwent hand-assisted laparoscopic surgeries, with no significant differences noted in the types of laparotomies or liver resections.

None of the patients in either cohort underwent conversion to open surgery. Short-term surgical outcomes, including operative time, blood loss, and severe morbidities (Clavien–Dindo grade ≥ IIIa) were statistically similar between cohorts. Cohort A had a statistically significantly shorter postoperative hospital stay than did Cohort O (median values: 9 and 11 days, respectively; $P = 0.0228$).

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Table 1 Participants' demographic and clinical characteristics are depicted

	O Cohort (*n* = 25)	A Cohort (*n* = 25)	*P* value
Age	73.0 (55.1–94.0)	72.0 (48.5–83.1)	0.4669
Sex (Male)	19 (76.0)	19 (76.0)	1.0000
ASA–PS (1/2/3)	0/18 (72.0)/7(28.0)	1 (4.0)/21 (84.0)/3 (12.0)	0.2890
Height(cm)	161.1 (139.6–177.0)	162 (139.6 − 177.2)	0.9536
Weight (kg)	59.8 (42.0–91.0)	61.6 (43.0–87.2)	0.4787
BMI	22.9 (17.3–31.9)	23.3 (18.6–31.1)	0.3084
Diseases (HCC/ICC/metastasis/ other)	13 (52.0)/3 (12.0)/9 (36.0)/0	11 (44.0)/1 (4.0)/11 (44.0)/2 (4.0)	0.4491
Type of liver resection (partial/≥ 1 section)	21 (84.0)/4 (16.0)	24 (96.0)/1 (4.0)	0.3487
Type of laparotomy (pure/HALS/ robot)	15 (60.0)/10 (40.0)/0	16 (64.0)/7 (28.0)/2 (8.0)	0.3880
Tumor size (mm)	22 (10–190)	20 (10–40)	0.1462
Number of resected tumors	1 (1–12)	1 (1–3)	0.5087
Fibrosis (0/1/2/3/4/unexamined)	7/7/3/3/1/4	1/4/1/3/2/14	0.4186
Preoperative serum laboratory examination results			
Alb (g/dL)	4.0 (3.1–4.8)	4.1 (3.4–4.9)	0.1336
T.Bil (mg/dL)	0.7 (0.4–1.8)	0.6 (0.3–1.3)	0.1867
AST (IU/L)	27 (13–77)	22 (13–48)	0.0947
ALT (IU/L)	22 (9–81)	18 (8–70)	0.5797
Creatinine (mg/dL)	0.83 (0.54–1.29)	0.78 (0.48–1.77)	0.9073
eGFR (mL/min/1.73m^2)	66.0 (35.2–114.4)	66.5 (30.0–117.1)	0.8386
Platelets (x10^4/uL)	18.5 (10.2–38.4)	17.7 (8.0–32.4)	0.9923
Prothrombin time (%)	98.8 (33.6–124.4)	97.2 (44.0–142.2)	0.7268
ICG-r15 (%)	11.7 (2.3–23.7)	9.1 (2.2–42.4)	0.1593
Operation time (min)	349 (216–735)	341 (143–639)	0.5869
Blood loss (g)	150 (4–880)	80 (1–630)	0.7268
Pringle maneuver (times)	5 (0–15)	5 (0–16)	0.5200

Data are given as numbers (n) (%) or median (range)

Abbreviations: *Alb* Albumin, *ALT* Alanine transaminase, *ASA–PS* American Society of Anesthesiologists–Physical Status, *AST* Aspartate transaminase, *BMI* Body mass index, *eGFR* Estimated glomerular filtration rate, *ICG-r15* Indocyanine green retention test at 15 min, *HALS* Hand-assisted laparoscopic surgery, *HCC* Hepatocellular carcinoma, *ICC* Intrahepatic cholangiocarcinoma, *T.Bil* Total bilirubin

Perioperative serum laboratory examination results and routine acetaminophen administration

To evaluate the safety of acetaminophen as postoperative analgesia for MIHs, perioperative serum laboratory examination results, reflective of and including hepatic and renal functions and systemic inflammation, were compared between the two cohorts. Perioperative liver function tests (AST, ALT, T. Bil, and PT) revealed an initial increase on the first postoperative day, followed by a gradual improvement over time (Fig. 2). No significant differences in the liver function tests were observed between the two cohorts on the first, third, fifth, and seventh postoperative days (Fig. 2a–d). Postoperative liver failure was not observed in any of the patients from either cohort. Additionally, renal function and systemic inflammatory markers were comparable between the two cohorts (Fig. 2e, f). No rehospitalizations due to liver failure were observed during the follow-up period.

Postoperative analgesia assessment

The efficacy of postoperative analgesia, comprising routine intravenous acetaminophen administration, was evaluated using the fentanyl doses, NRS scores, and incidence rates of PONV (Table 2). No significant differences in the total fentanyl doses were observed between the two cohorts. However, the median number of rescue doses was statistically significantly higher in Cohort O (median value = 6 doses) than in Cohort A (median value = 0 doses) (*P* = 0.0017). The rescue doses were generally administered before the reduction or discontinuation of opioids.

The NRS scores at rest on the first postoperative day were statistically significantly lower in Cohort A (median score = 2) than in Cohort O (median score = 4) (*P* = 0.0005). Similarly, the NRS scores during movement on the second postoperative day were statistically significantly lower in Cohort A (median score = 3) than in Cohort O (median score = 5) (*P* = 0.0195). In Cohorts O and A respectively, 17 (68%) and 20 patients (80%) underwent PNBs, with no significant differences observed.

In a sub-cohort analysis of patients who underwent PNBs that might have affected postoperative pain, the median number of rescue doses was statistically significantly higher in Cohort O (median value: three doses) than in Cohort A (median value: one dose) (*P* = 0.0329). Moreover, the NRS scores at rest on the first postoperative day were statistically significantly higher in Cohort O (median score = 4) than in Cohort A (median score = 2) (*P* = 0.0004).

Nine and eight patients in Cohorts O and A required fentanyl reduction or discontinuation due to PONV, respectively. No significant differences in the PONV frequency, anti-emetic use, or fentanyl dose reduction were observed between the two cohorts.

Assessment of analgesia after reduction or discontinuation of fentanyl

The analgesic efficacy after the reduction or discontinuation of fentanyl was evaluated (Table 3). Of all the patients, some in Cohort O required frequent rescue
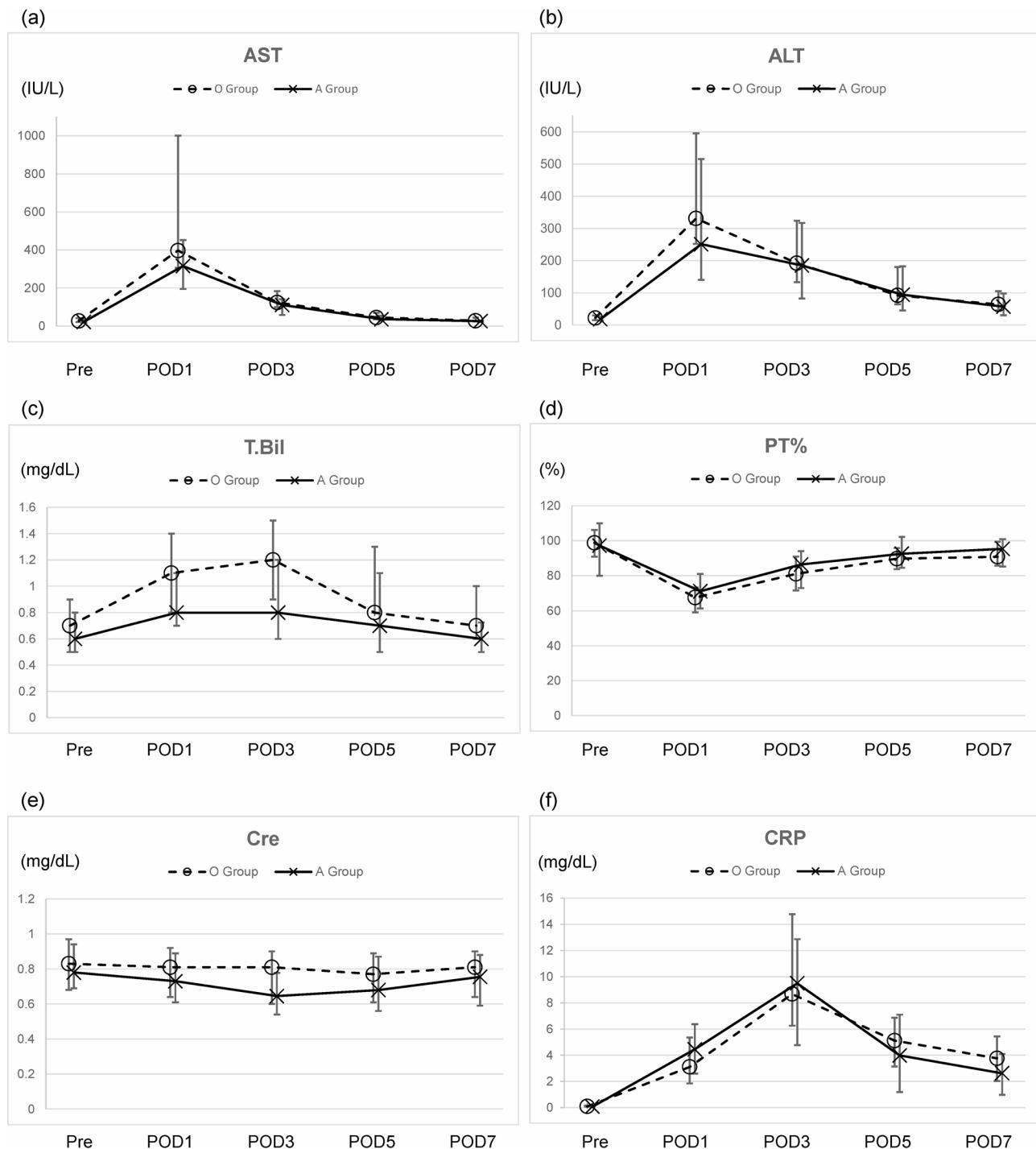
Fig. 2 Perioperative serum laboratory examination trends are shown. Hepatic and renal functions and systemic inflammation have been evaluated using serum laboratory examination results on preoperative and the first, third, fifth, and seventh postoperative days. In (**a**)–(**d**), abnormal values are observed in the early postoperative period; however, these have quickly improved and do not differ between the two cohorts. Furthermore, renal function and systemic inflammation do not differ between the two cohorts. Abbreviations: (a) AST, aspartate transaminase; (b) ALT, alanine transaminase; (c) T. Bil, total bilirubin; (d) PT, prothrombin time; (e) Cre, creatinine; (f) CRP, C-reactive protein; (g) POD, postoperative day

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Table 2 Fentanyl dosage, pain scale, and short-term outcomes

	Cohort O (n = 25)	Cohort A (n = 25)	P value
Intraoperative dose of fentanyl (ug)	450 (250–800)	400 (150–1000)	0.7405
Postoperative dose of fentanyl (ug)	1500 (665–2000)	1500 (100–2000)	0.7770
Initial dosing rate of fentanyl(ug/h)	25.0 (12.5–45.0)	27.5 (12.5–42.5)	0.7106
Sum of rescue doses	6 (0–16)	0 (0–8)	0.0017
Reduction or discontinuation of fentanyl (+)	9 (36.0)	8 (32.0)	1.0000
Peripheral nerve block (+)	17 (68.0)	20 (80.0)	0.5202
POD1NRS			
At rest	4 (1–7)	2 (0–5)	0.0005
During movement	5 (1–10)	5 (1–10)	0.2319
POD2NRS			
At rest	2 (0–6)	2 (0–3)	0.1879
During movement	5 (0–10)	3 (1–8)	0.0195
PONV (+)	21 (84.0)	17 (68.0)	0.3209
Sum of anti-emetic agent doses	1 (0–9)	1 (0–5)	0.5781
Delirium	4 (16.0)/21 (84.0)	2 (8.0)/23 (92.0)	0.6671
Morbidity (C–D grade ≥ 3)	3 (12.0)/22 (88.0)	1 (4.0)/24 (96.0)	0.6092
Time-to-oral intake (days)	3 (2–11)	3 (2–3)	0.1497
Time-to-ambulation (days)	1 (1–1)	1 (1–1)	1.000
Length of postoperative hospital stay (days)	11 (8–19)	9 (7–114)	0.0228

Median (range) n (%)

Abbreviations: *C–D* Clavien–Dindo, *NRS* Numerical rating scale, *POD* Postoperative day, *PONV* Postoperative nausea and vomiting

Table 3 Postoperative nausea and vomiting and pain scale post-fentanyl reduction

	Cohort O (n = 9)	Cohort A (n = 8)	P value
Sum of rescue doses post-fentanyl reduction	0 (0–7)	0 (0–1)	0.2341
PONV(+)	6 (66.7)	3 (37.5)	0.3469
NRS			
At rest	2 (0–4)	1 (1–4)	0.2164
During movement	4 (2–8)	2 (1–4)	0.0305
Increase of NRS			
At rest	2 (22.2)	2 (25.0)	1.0000
During movement	3 (33.3)	0	0.2059

Data are given as numbers (n) (%) or median (range)

Abbreviations: *NRS* Numerical rating scale, *PONV* Postoperative nausea and vomiting

doses of fentanyl. However, no significant differences were observed between the two cohorts regarding the number of rescue doses required. Notably, the NRS scores during movement were statistically significantly lower in Cohort A (median score = 2) than in Cohort O (median score = 4) after fentanyl reduction (*P* = 0.0305). patients in Cohort A did not report worsening of pain

after fentanyl reduction; however, three patients in Cohort O reported increased pain during movement.

Reduction of total fentanyl dose and risk factors for PONV

Table 4 presents the results of the univariate and multivariate analyses of PONV risk factors. The univariate analysis identified higher intraoperative fentanyl doses as a significant risk factor for PONV (odds ratio [OR], 1.0042; 95% confidence interval [CI], 1.0003–1.0081, *P* = 0.0257). However, the multivariate analysis did not identify any independent risk factors. Intraoperative factors (OR, 2.600; 95% CI, 1.095–6.687, *P* = 0.030), including increased blood loss (OR, 1.0045; 95% CI, 1.0007–1.00082, *P* = 0.0066), hand-assisted laparoscopic surgery (OR, 4.3922; 95% CI, 1.0600–18.1999, *P* = 0.0413), and larger tumor diameter (OR, 1.0440; 95% CI, 1.0023–1.9835, *P* = 0.217), were correlated with a higher number of intraoperative fentanyl doses (Table 5).

Discussion

Alignment with PROSPECT guidelines

Our findings align with several recommendations from the PROSPECT guidelines for liver resection, including the use of multimodal analgesia and the incorporation of non-opioid agents such as acetaminophen [16]. While the guidelines recommend thoracic epidural analgesia, challenges involving perioperative pain management in liver resection, particularly regarding the administration of epidural anesthesia and opioids, still exist due to possible complications, such as hemorrhage and opioid-related adverse effects. The potential hepatotoxicity of acetaminophen has been a major concern in liver surgery [15, 16]. Nonetheless, our findings support the safety and efficacy of acetaminophen as part of a multimodal analgesia protocol in MIH.

Safety of acetaminophen in MIH

First, the safety of acetaminophen was evaluated using perioperative serum laboratory examination results to confirm the presence or absence of liver failure (Fig. 2). Although acetaminophen is widely used for postoperative analgesia [5]it is metabolized in the liver and may cause hepatotoxicity, making liver surgeons cautious about its administration [17]. Nevertheless, intravenous acetaminophen is increasingly considered a valuable component of multimodal analgesia in hepatectomy, particularly within ERAS protocols [15]. However, few studies exist regarding this administration as part of post-liver resection multimodal analgesia. Recently, the safety of acetaminophen for post-open hepatectomy analgesia has been revealed [15, 16]. Hidaka et al. have assessed hepatic function using comprehensive measures, such as serum laboratory examinations and grading of fibrosis, confirming that acetaminophen does not exacerbate liver

Table 4 Univariate and multivariate analyses of risk factors for postoperative nausea and vomiting

	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Cohorts (O/A)	2.4706	0.6341–9.6253	0.1924			
Sex (M/F)	0.5600	0.1043–3.0081	0.4990			
Age	1.0223	0.9541–1.0954	0.5310			
History of PONV/motion sickness	-	-	-			
Smoking status (+/-)	0.2471	0.0476–1.2830	0.0962	0.3701	0.0647–2.1173	0.2640
Duration of anesthesia	0.9966	0.9915–1.0018	0.1977			
Use of volatile anesthetics	-	-	-			
Use of nitrous oxide	-	-	-			
Intraoperative fentanyl doses	1.0042	1.0003–1.0081	0.0257	1.0034	0.9994–1.0074	0.0831
Postoperative fentanyl doses	0.9671	0.8859–1.0558	0.4346			

Abbreviations: *CI* Confidence interval, *OR* Odds ratio, *PONV* Postoperative nausea and vomiting

Table 5 Univariate and multivariate analyses of risk factors for increased intraoperative fentanyl doses

	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Cohorts (O/A)	0.8438	0.3778–3.7181	0.7709			
Sex (M/F)	1.2245	0.3260–4.5996	0.7642			
Age	0.9551	0.8944–1.1020	0.1549			
Operation time (min)	1.0046	0.9994–1.0100	0.0648			
Blood loss (g)	1.0045	1.0007–1.0082	0.0066	1.0026	0.9982–1.0070	0.2260
Type of laparotomy (HALS/other)	4.3922	1.0600–18.1999	0.0413	2.3106	0.3952–13.5079	0.3526
Tumor size (mm)	1.0440	1.0023–1.9835	0.0217	1.0336	0.9775–1.0930	0.1289
Number of resected tumors	2.1054	0.7051–6.2863	0.0553			
Pringle maneuver (times)	0.9681	0.8371–1.1195	0.6621			
Peripheral nerve block (+/-)	1.0268	02798–3.7674	0.9682			

Abbreviations: *CI* Confidence interval, *HALS H*and-assisted laparoscopic surgery, *OR* Odds ratio

injury post hepatectomy [14]. Based on these findings, we hypothesized that acetaminophen could be administered more safely in MIH, which is more likely to involve less extensive liver resections compared to open hepatectomy. Our results support this hypothesis and align with the findings of Hidaka et al., suggesting that intravenous acetaminophen can be safely used in MIH, even among patients with potentially compromised hepatic function.

Pain management and opioid-sparing effects
Second, our study expanded on the work of Hidaka et al. by providing objective measures of postoperative pain management using the NRS. Pain is inherently subjective and influenced by various unquantifiable factors, which makes consistent evaluation challenging. To address this, we employed the NRS to provide a standardized and reproducible measure of pain intensity. In particular, we revealed the reduced requirements for opioid rescue doses in patients receiving routine acetaminophen. This finding has been shown in other studies regarding gastrointestinal surgery [18–21]but has not been thoroughly explored concerning MIHs. Thus, this study finding provides an important contribution to the understanding of the role of acetaminophen in postoperative pain management after MIHs.

Impact on opioid rescue doses and hospital stay
Third, we demonstrated that acetaminophen statistically significantly reduced the number of fentanyl rescue doses required during the early postoperative phase, particularly during movement, which is commonly the most challenging period for pain management. Thus, these findings revealed that regular acetaminophen intravenous administration may facilitate early mobilization and reduce postoperative hospital stays, aligning with the results of previous studies regarding other gastrointestinal surgeries [21, 22]. These results indicate that routine intravenous administration of acetaminophen may be effective for post-MIH analgesia. Furthermore, in recent years, as the usefulness of MIHs has been established and their development and adoption are expected to increase [13]the reduction in postoperative hospital stays may contribute to a more efficient use of medical resources and potential decrease in healthcare costs [23, 24]. However, the total opioid dose did not differ. This may be because the total dose was predetermined at the time of iv-PCA setting and because dose reductions for reasons other than PONV—such as low NRS scores—were not observed. Further investigation is warranted. Additionally, since elderly patients were included in this study,

there was a tendency toward longer hospital stays, which also warrants further investigation.

Effects on opioid-related adverse events

Acetaminophen effectively reduced the need for opioid rescue doses; however, its impact regarding lesser opioid-related adverse effects, such as PONV, was not as pronounced as in studies involving other gastrointestinal surgeries [25]. A possible explanation for this is that the total fentanyl dose, rather than the number of rescue doses, plays a more clinically significant role in the development of PONV. Analgesia and nausea are controlled by distinct physiological mechanisms and high plasma concentrations of fentanyl-stimulated μ-opioid receptors in the medulla and chemoreceptor trigger zone (CTZ), triggering nausea [25, 26]. In our study, acetaminophen appeared to reduce the requirement for rescue fentanyl doses; however, the total intraoperative and postoperative opioid doses were comparable between the cohorts, which may explain why we did not observe a statistically significant reduction in PONV. Further analysis revealed that the total intraoperative opioid dose was a statistically significant contributor to the development of PONV. Intraoperative opioid administration typically involves rapid bolus dosing, which can result in sharp increases in plasma opioid concentrations, overstimulation of medullary CTZ, and the induction of nausea and vomiting [27]. Based on these findings, we are planning a prospective clinical trial to determine whether greater reductions in the total opioid dose, achieved through alternative analgesic strategies or higher doses of acetaminophen, could result in more pronounced reductions in PONV, thus maintaining pain management for MIH.

Enhanced pain control with PNBs

Our sub-cohort analysis revealed that, particularly among patients receiving PNBs, those administered routine acetaminophen had lower pain scores, showing that acetaminophen may enhance pain management beyond the effects of PNBs alone, which are known for their strong analgesic effect during the early postoperative period of abdominal surgery [28]. Studies have indicated that acetaminophen acts peripherally by inhibiting cyclooxygenase enzymes and centrally by engaging the serotonergic pathways [29]. Therefore, combined with the local action of PNBs, acetaminophen may provide more comprehensive pain management. ERAS protocols, including multimodal analgesia, have demonstrated improved postoperative outcomes in liver resection [30]. Incorporating acetaminophen into these protocols may further optimize postoperative pain control and enhance recovery.

Study limitations and future directions

Study limitations include the single-center and small-sample design, as well as potential biases inherent in the retrospective nature of the study and the lack of randomization. Factors such as the predominance of elderly patients, institution-specific perioperative management practices (including anesthetic protocols and timing of oral intake), the unclear effects on patients with severe hepatic impairment, and the interaction with other multimodal analgesic strategies remain uncertain. Consequently, the ability to control for selection bias and unmeasured confounding factors is limited. Future research should comprise multicenter, prospective studies with larger cohorts to validate and generalize these findings and further explore the optimal dosing and timing of acetaminophen administration regarding multimodal analgesia for MIHs. Finally, the study predominantly consisted of patients who had undergone partial hepatectomies. Therefore, the safety of acetaminophen in the setting of major liver resections performed via MIH requires further investigation.

Conclusions

In conclusion, multimodal analgesia comprising the routine intravenous administration of acetaminophen could be effective and safe post-MIHs, without adverse effects regarding hepatic function.

Authors' contributions
KF, MN and YT designed this study. KF, MN, YT, YS, HM, YK, YN, YW, ST, NM, MI, HT, TI, TU and HN collected and analyzed the data for the study. KF and MN prepared the manuscript. HN supervised the study. All authors are in agreement with the contents of the manuscript.

Data availability
Data available on request from the authors: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study has been approved by the Ethics Committee (EC) of Yamaguchi University Hospital, with the EC approval number: 2024-020. Moreover, this study has been conducted in accordance with the principles of the World Medical Association Declaration of Helsinki involving human patients (as revised in Brazil 2013).

Consent for publication
Consent to Publish declaration: not applicable.

Competing interests
The authors declare no competing interests.

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