Research Square

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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. Multimodal therapies for postoperative pain management commonly comprise acetaminophen. However, the safety and efficacy of acetaminophen for postoperative analgesia in minimally invasive hepatectomy remains unestablished due to its hepatic metabolism. This study aimed to evaluate the safety and analgesic efficacy of routine intravenous acetaminophen administration following MIH.

Methods

The data of consecutive 50 participants who had undergone MIH were retrospectively analyzed. Regarding postoperative analgesia, participants were assigned 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 statistically 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 lower NRS scores compared with 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 the routine intravenous acetaminophen administration could be safe and effective after minimally invasive hepatectomy, without adverse effects regarding hepatic function.

Background

Liver resection is technically challenging due to the liver's complex anatomy and rich blood supply[1]. Effective post-operative pain management is essential for improving surgical outcomes[2]. 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[3, 4].

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[5–7]. 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)[8, 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]. However, the safety and efficacy of acetaminophen administration post-minimally invasive hepatectomy (MIH) has not been fully established. Moreover, few studies have objectively assessed an improvement in postoperative pain management with acetaminophen administration[13, 14]. 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 participants (as revised in Brazil 2013). Written informed consent was obtained from the participants for the collection of their samples and publication of their de-identified data and images.

Participants and Methods

In this retrospective single-center cohort study, 50 consecutive participants 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 participants underwent peripheral nerve blocks (PNBs) during anesthetic management. All participants were managed with continuous intravenous fentanyl via intravenous patient-controlled postoperative analgesia. Dosages and rates had been calibrated by the anesthesiologist, according to the age and

weight of each participant, 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.

The participants were divided into two cohorts: Cohort O (opioids-alone, without the routine administration of acetaminophen) and Cohort A (with the regular administration of acetaminophen). Regarding Cohort A, acetaminophen was administered every 6 h, until 48 h postoperatively, as per the manufacturer's protocol (body weight [BW] ≥ 50 kg: 1000 mg/dose; BW < 50 kg: 15 mg/kg/dose) (Fig. 1).

Postoperative pain was evaluated for 2 days postoperatively, using a Numerical Rating Scale (NRS) at rest and during movement. 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 were evaluated for safety and adverse effects. Hepatic function was monitored using serum laboratory examinations on the first, third, fifth, and seventh postoperative days. Aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (T. Bil), and prothrombin time (PT) levels were measured to evaluate the potential hepatotoxic effects of acetaminophen.

Statistical analyses

The clinicopathological factors of Cohorts O and A were compared. Clinicopathological factors were analyzed using the Mann–Whitney U, Wilcoxon, and chi-square tests; while univariate survival analyses were performed using the Cox proportional hazards regression model. The cut-off value for the intraoperative fentanyl dose was determined using a receiver operating characteristic curve analysis. Participants 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 participants 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 participants in Cohorts O and A, respectively, underwent hand-assisted laparoscopic surgeries, with no statistically significant differences noted in the types of laparotomies or liver resections.

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
Median (range) n (%).			

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.

	O Cohort (n = 25)	A Cohort (n = 25)	P value
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
Median (range) n (%).			
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.			

None of the participants 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).

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 statistically 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 participants from either cohort. Additionally, renal function and systemic inflammatory markers were comparable between the two cohorts (Fig. 2e, f).

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 statistically 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).

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.			

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 participants (80%) underwent PNBs, with no statistically significant differences observed.

In a sub-cohort analysis of participants 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 participants in Cohorts O and A required fentanyl reduction or discontinuation due to PONV, respectively. No statistically 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 participants, some in Cohort O required frequent rescue doses of fentanyl. However, no statistically 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). Participants in Cohort A did not report worsening of pain after fentanyl reduction; however, three participants in Cohort O reported increased pain during movement.

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)/7 (77.8)	2 (25.0)/6 (75.0)	1.0000
during movement	3 (33.3)/6 (66.7)	0/8 (100.0)	0.2059
Median (range) n (%).			
Abbreviations: NRS = numerical rating scale; PONV = postoperative nausea and vomiting.			

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 (P = 0.0257). However, the multivariate analysis did not identify any independent risk factors. Intraoperative factors, including increased blood loss, hand-assisted laparoscopic surgery, and larger tumor diameter, were correlated with a higher number of intraoperative fentanyl doses (Table 5).

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	0.9923–1.9835	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 = hand-assisted laparoscopic surgery; OR = odds ratio.

Discussion

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[14, 15]. Nonetheless, our study findings highlight the safety and efficacy thereof when used as part of a multimodal analgesia protocol for MIHs.

First, the safety of acetaminophen was evaluated using perioperative serum laboratory examination results to confirm the presence or absence of liver failure (Fig. 2). Acetaminophen is commonly used as postoperative analgesia[4]. However, acetaminophen is metabolized in the liver and can potentially cause hepatotoxicity, causing liver surgeons to exercise caution regarding its administration[16]. Consequently,

multimodal analgesia comprising the intravenous administration of acetaminophen could be a feasible approach. 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[14, 15]. 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 injury post-minimally invasive liver surgery[13]. Our findings are consistent with those of Hidaka et al., further supporting the hypothesis that acetaminophen can be safely administered to patients undergoing MIHs, particularly to those with potentially compromised hepatic function.

Second, our study expanded on the work of Hidaka et al. by providing objective measures of postoperative pain management using the NRS, particularly revealing the reduced requirements for opioid rescue doses in patients receiving routine acetaminophen. This finding has been shown in other studies regarding gastrointestinal surgery[17–20], 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.

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[20–22]. 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, the reduction in postoperative hospital stays may contribute to a more efficient use of medical resources and potential decrease in healthcare costs[23, 24].

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.

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, 30]. Therefore, combined with the local action of PNBs, acetaminophen may provide more comprehensive pain management.

Study limitations include the single-center, small-sample design; in addition to the potential biases inherent to the retrospective nature of the study. Future research should comprise multicenter, prospective studies with larger cohorts to validate these findings and further explore the optimal dosing and timing of acetaminophen administration regarding multimodal analgesia for MIHs. Finally, the study predominantly consisted of participants who had undergone partial hepatectomies. Therefore, the safety of acetaminophen during major liver resections using minimally invasive techniques, 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.

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 participants (as revised in Brazil 2013).

Patient Consent Statement

Written informed consent was obtained from the participants for the collection of their samples and publication of their de-identified data and images.

Consent for publication

Consent to Publish declaration: not applicable

Availability of data and materials

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.

Competing interests

The authors declare that they have no competing interests.

Conflict of Interest Disclosure

Authors declare no Conflict of Interests for this article.

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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.

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Figures

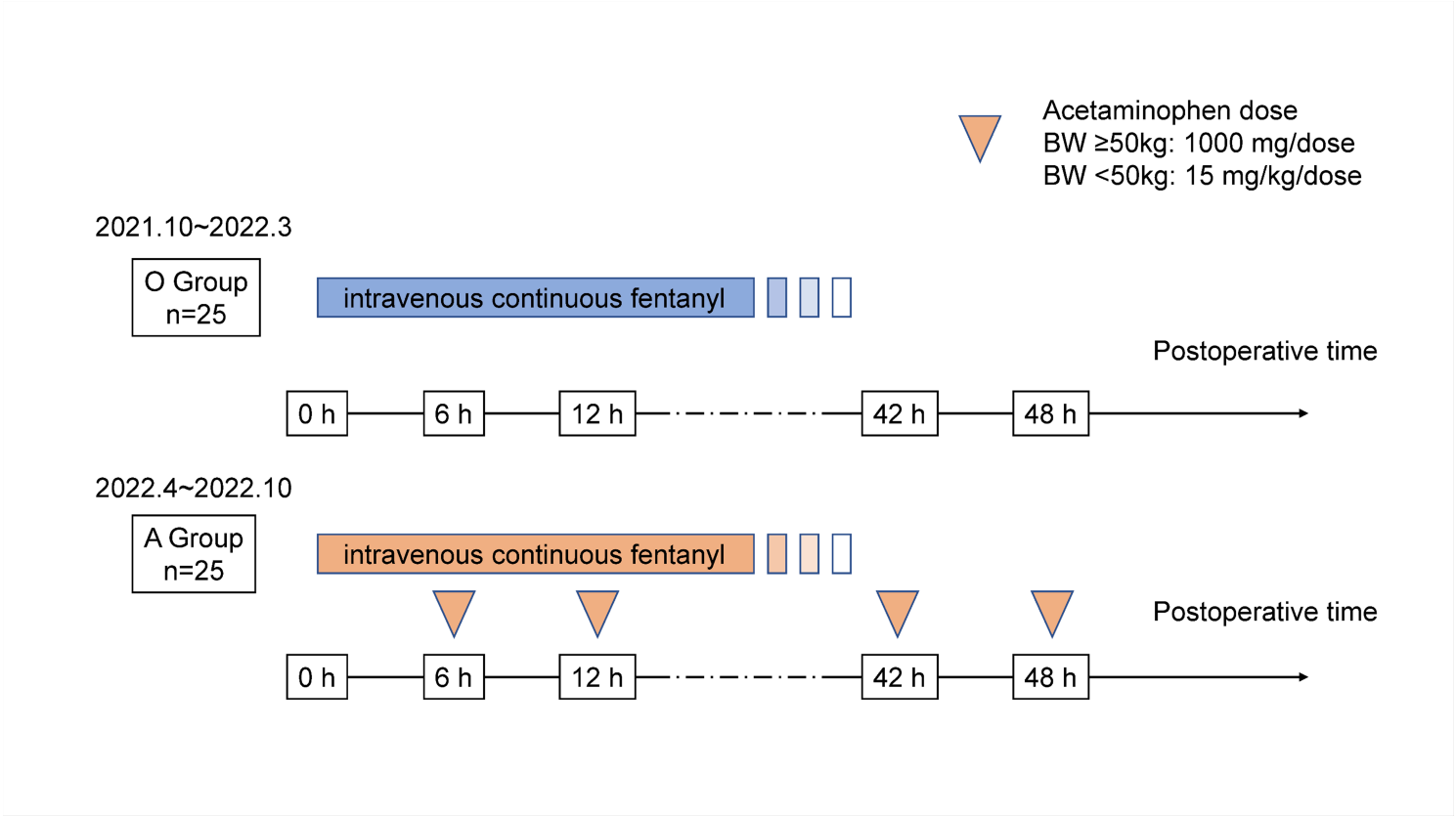


Figure 1

Study design is depicted

Data of the study participants from the period of October 2021 to October 2022 have been included. The participants 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

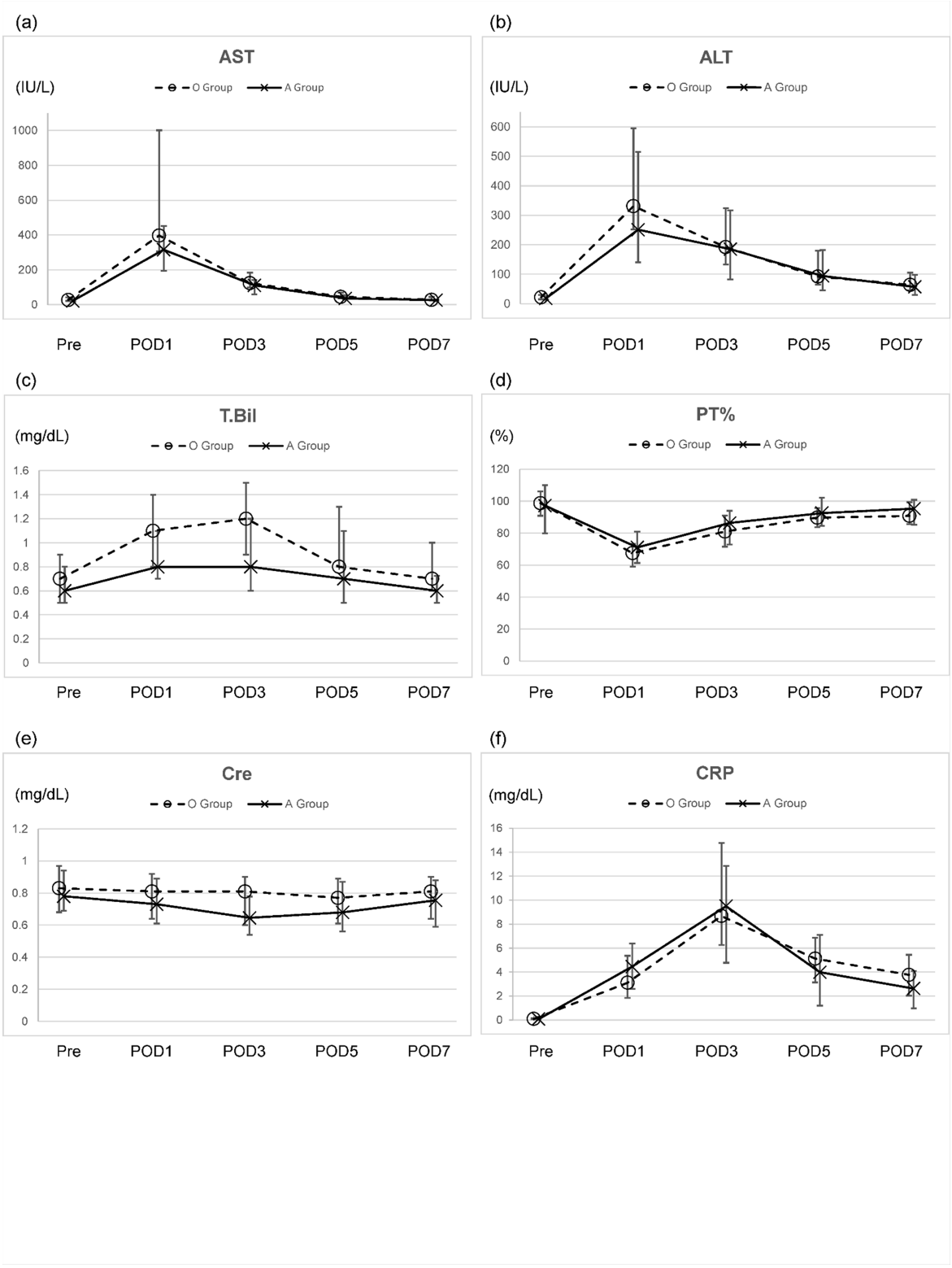


Figure 2

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.