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Analgesic Safety of Periodic Intravenous Infusion of Acetaminophen After Hepatectomy: A Propensity Score Matching Analysis

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ABSTRACT

Background and Aim: *Acetaminophen is an often-used analgesic for management of postoperative pain; it is not associated with hypomotility of the gastrointestinal tract or postoperative nausea and vomiting. It may, however, negatively affect liver function. Thus, acetaminophen is rarely used after hepatectomy and there are few studies pertaining to the analgesic safety of such use. We investigated the analgesic safety of periodic intravenous infusion of acetaminophen following hepatectomy.*

Patients and Methods: *The study included 92 patients who had undergone hepatectomy without biliary reconstruction at St. Marianna University Hospital between January 2014 and November 2018. These patients were identified from among a larger group of patients, and propensity score matching allowed for the creation of two study groups: 46 patients who had undergone periodic intravenous infusion of acetaminophen for postoperative pain management (Group A), and 46 control patients who had undergone bolus injections of the non-steroidal anti-inflammatory drug upon request (Group C). The two groups were then compared retrospectively in terms of clinical characteristics; operative variables; details regarding postoperative analgesia; concentrations of serum liver enzymes (total bilirubin [TBL], aminotransaminases aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP] and gamma-glutamyl transpeptidase [γGTP]) determined preoperatively, on postoperative days (PODs) 1, 3 and 7, and between PODs 14 and 28; and in-hospital outcomes and complications.*

Results: *Patients' clinical characteristics and operative variables did not differ between the two groups. Of the liver enzymes, only the serum γGTP concentrations observed on POD 7 and POD 14 differed significantly ($p=0.003$ and $p=0.017$, respectively). No patient suffered CTCAE Grade ≥ 3 hepatic failure, and there was no mortality.*

Conclusion: *Results of our study indicate that periodic intravenous infusion of acetaminophen after hepatectomy is a safe means of managing patients' postoperative pain.*

Keywords

Acetaminophen, Hepatectomy, Periodic intravenous administration.

Introduction

Despite the widespread availability of medications and techniques used for pain management, we cannot ensure that complications will not arise in response to agents given to prevent or manage postoperative pain. Acetaminophen is an important analgesic agent for management of postoperative pain because side effects are few and because it can be used in asthmatics. The utility of regularly scheduled intravenous administration of acetaminophen in patients who have undergone digestive surgery has been reported [1,2]. However, because acetaminophen administered in high doses is known to negatively affect liver function, it is rarely used for relief of pain following hepatectomy. There has not been adequate study, however, of the analgesic safety of intravenous infusion of acetaminophen after hepatectomy. Thus, we conducted a retrospective study in which investigated the analgesic safety of periodic intravenous infusion of acetaminophen following

hepatectomy.

Patients and Methods

Patient selection and propensity score matching

We selected, by means of propensity score matching, 92 patients to be included in the study. These patients were identified from among 137 patients who had undergone hepatectomy without biliary reconstruction at St. Marianna University School of Medicine Hospital between January 2014 and November 2018. Fifty-seven of the 137 patients had undergone hepatectomy before June 2016, .i.e., before we introduced periodic intravenous acetaminophen infusion for management of post-hepatectomy pain. Eighty of the 137 patients had undergone hepatectomy after we introduced the acetaminophen infusion protocol, but of these 80, 5 suffered a cut surface abscess postoperatively, and 1 suffered postoperative bleeding. Thus, 74 of the 80 patients who had undergone periodic intravenous acetaminophen infusion were considered for the study. Propensity scores were derived from a multiple logistic regression model that included age, sex, body mass index [BMI], clinical diagnosis, Child-Pugh classification, presence of liver cirrhosis, whether the patient had undergone preoperative chemotherapy, the surgical procedure, operation time and intraoperative blood loss. Use of a 1:1 nearest neighbor matching algorithm issued in the creation of 46 patient pairs. The pairs were then split into two groups: patients who did not undergo periodic postoperative acetaminophen infusion, i.e., control group (Group C, n=46), and patients who did undergo the periodic acetaminophen infusion. i.e., acetaminophen group (Group A, n=46) (Figure 1).

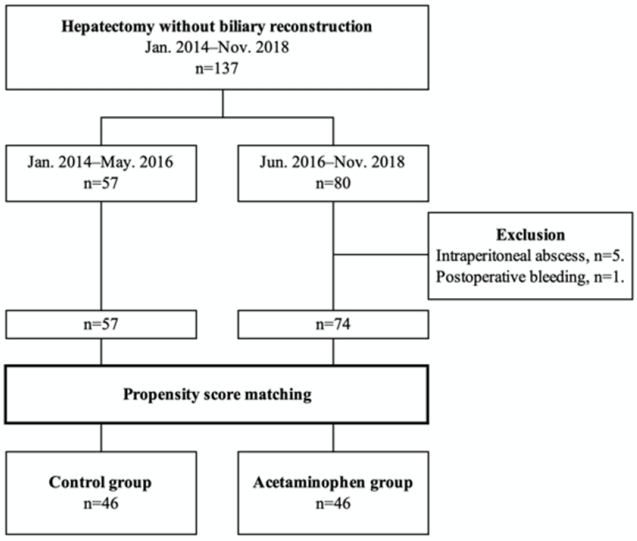


Figure 1: Flow diagram showing allotment of patients to study groups by propensity score matching.

Postoperative analgesic regimens

The postoperative analgesic regimens are shown schematically in Figure 2. In Group C, postoperative pain was controlled by bolus infusions, on postoperative days (PODs) 4 and 5, of a non-steroidal anti-inflammatory drug (NSAID), and then by oral administration, depending on individual patients' pain intensity. In Group A, acetaminophen (Acelio Intravenous Injection®; TERUMO Co. Ltd., Tokyo, Japan) was administered intravenously at 1000 mg 3 to 6 hours after the surgery and then repeated every 8 hours for patients weighing ≥ 50 kg or at 15 mg/kg and then repeated every 8 hours for patients weighing <50 kg. In this group, the periodic infusion was continued until POD 4 or 5, depending on the pain intensity. For all patients, thoracic epidural anesthesia was begun at the time of recovery from general anesthesia and performed by continuous infusion of 300 mL of 0.25% levobupivacaine (280–290 mL) and fentanyl (5–10 ampules, 0.1 mg/2 mL) at 2-6 mL/hour, depending on the intensity of the patient's pain, and patient-controlled rescue anesthesia was made available.

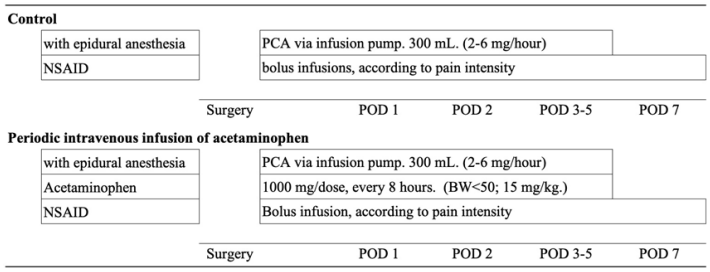


Figure 2: Postoperative analgesic regimens.
PCA patient-controlled anesthesia, NSAID nonsteroidal anti-inflammatory drug, BW body weight.

Data collection and assessment of outcomes

To assess the analgesic safety of periodic acetaminophen, we obtained, from records of patients in both groups, patients' clinical characteristics; operative variables; details regarding postoperative analgesia; concentrations of serum liver enzymes (total bilirubin [TBL], aminotransaminases aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP] and gamma-glutamyl transpeptidase [γGTP]) determined before the surgery, on PODs 1, 3 and 7, and between POD 14 and 28; and in-hospital clinical outcomes and complications. Complications were defined as postoperative events of Clavien-Dindo (C-D) grade ≥II [3,4]. Postoperative hepatic failure was defined, according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, as an inability of the liver to metabolize chemicals in the body [5], marked by abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase and/or prolongation of prothrombin time. Drug-induced liver injury [DILI] was established on the basis of Hy's Law (Table 1) [6]. Grade ≥3 events (asterixis, mild encephalopathy, DILI, limited self-care); Grade 4 events (life-threatening sequelae, moderate to severe encephalopathy, coma); and Grade 5 events (death) were recorded as complications.

Hy's Law cases have the following three components:	
1.	The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the upper limits of normal (ULN) of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2.	Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).
3.	No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Table 1: Hy's Law for drug-induced liver injury*.
*From Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Page 5, July 2009.

Statistical analyses

Data are shown as mean (± SD or SE) values. Between-group differences were analyzed by Pearson's chi-square test, Student's t-test, Fisher's exact test, Wilcoxon test or Mann-Whitney U test, as appropriate. All statistical analyses were performed with JMP® 14 (SAS Institute Inc., Cary, NC, USA), and $p<0.05$ was considered significant.

Results

Patient characteristics and operative variables

Patient characteristics and operative variables are shown per study group in Table 2. The groups were similar in terms of age, sex, BMI, clinical diagnoses, Child-Pugh class, liver cirrhosis, preoperative chemotherapy, surgical procedure and operative variables including operation time and blood loss volume.

		Group C (n=46)	Group A (n=46)	p Value
Age (years)		67.1 ± 1.7	66.8 ± 1.7	0.919
Male sex		35	33	0.635
Body mass index (kg/m²)		23.0 ± 0.5	22.7 ± 0.5	0.612
Clinical diagnosis	HCC	22	22	0.580
	CCC	3	5	
	Liver metastasis	15	18	
	Other	3	1	
Child-Pugh classification	A/B	45/1	45/1	1.000
	Liver cirrhosis	6	5	0.748
	Pre-operative chemotherapy	7	7	1.000
Surgical procedure	Anatomical resection	20	22	0.676
	Partial resection/lateral segmentectomy	26	24	
Operation time (minutes)		258.2 ± 15.6	242.6 ± 12.3	0.435
Number of Pringle procedures		4.2 ± 0.4	3.7 ± 0.4	0.449
Intraoperative blood loss (mL)		470.1 ± 66.5	443.6 ± 72.4	0.788

Table 2: Patients' clinical characteristics and operative variables, per group.

Mean ± SE values or number of patients are shown, unless otherwise indicated.

Group C control group, Group A acetaminophen group, HCC hepatocellular carcinoma, CCC cholangiocellular carcinoma.

Details of postoperative analgesia

Details of the postoperative analgesia are shown per group in Table 3. Epidural anesthesia was given to patients in both groups — for 3.6 days in Group C and 5.1 days in Group A ($p<0.001$). In Group A, acetaminophen was injected periodically 12.5 times over a period of 4.2 days.

In Group C, the periodic analgesic was injected 0 times over a period of 0 days. During the first 72 hours after hepatectomy, Group A patients received significantly fewer bolus injections of the analgesic than did Group C patients (0.5 injections vs 1.7 injections, respectively); $p<0.0001$).

		Group C (n=46)	Group A (n=46)	p Value
Periodic infusion of acetaminophen	Period (days)	0	4.2 ± 0.1	
	Total infusion times	0	12.5 ± 0.4	
Period of epidural anesthesia (days)		3.6 ± 0.2	5.1 ± 0.2	<0.0001
Bolus injections of the analgesic during the first 72 hours after surgery		1.7 (SD 1.6)	0.5 (SD 1.1)	<0.0001

Table 3: Details of postoperative analgesia, per group. Mean ± SE values or number of patients are shown, unless otherwise indicated.

Group C control group, Group A acetaminophen group.

Postoperative liver enzyme concentrations

Concentrations of TBL, AST, ALT, ALP and γGTP are shown per group in Figure 3. The concentrations were highest on POD 2 and decreased gradually thereafter. The TBL (Figure 3-a) and ALT (Figure 3-c) concentrations did not differ significantly between the two groups. The POD 7 AST (Figure 3-b) concentration was significantly higher in Group A than in Group C (34.9 vs 26.6 U/L, respectively; $p=0.027$) but was not much above the upper limit of normal (ULN; 32 U/L).

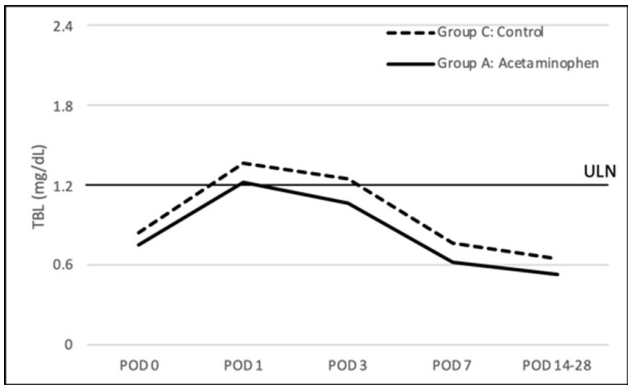
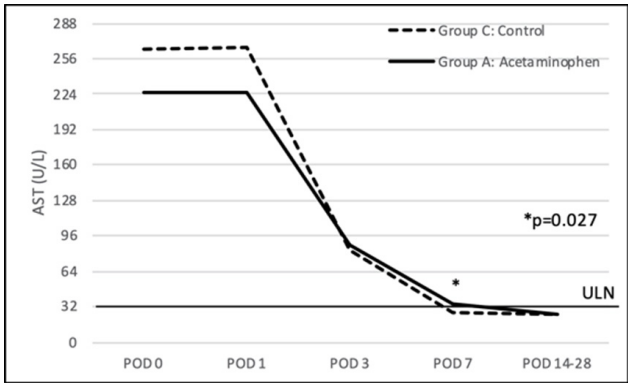


Figure 3: Pre- and post-operative liver enzyme concentrations.

(a) TBL: POD postoperative day, TBL total bilirubin, ULN upper limit of normal.

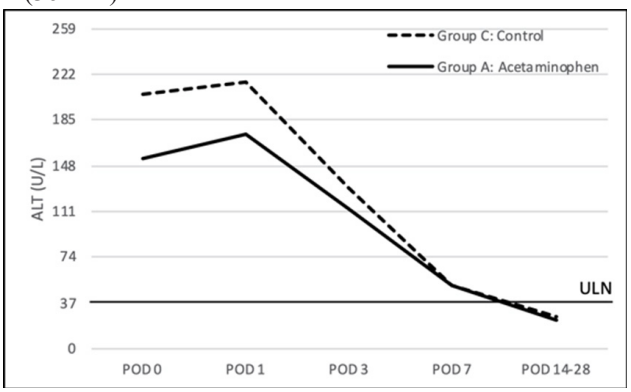
In both groups, the TBL concentration was highest on POD 2 and then decreased gradually. The TBL concentrations did not differ significantly between groups.



(b) AST: AST aspartate aminotransferase, POD postoperative day, ULN upper limit of normal.

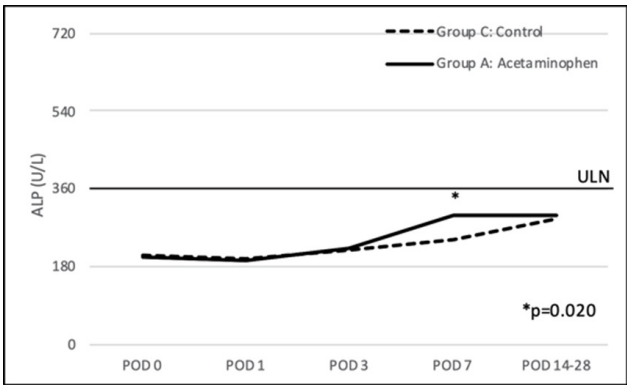
In both groups, the AST concentration was highest on POD 2 and then decreased gradually. The POD 7 AST level was significantly higher in Group A than in Group C, but both were close to the upper limit of normal.

The POD 7ALP concentration (Figure 3-d) was significantly higher in Group A than in Group C (297.0 vs 242.6 U/L, respectively; p=0.020), but the ALP concentration never increased beyond the ULN (360 U/L) in either group. The POD 7 γGTP concentration (Figure 3-e) was significantly higher in Group A than in Group C (142.4 vs 54.9 U/L, respectively; p=0.0030). The POD 14–28 γGTP concentration was also significantly higher in Group A than in Group C (77.7 vs 51.0 U/L, respectively; p=0.017), and γGTP was the only liver enzyme that remained consistently above the ULN (36 U/L).



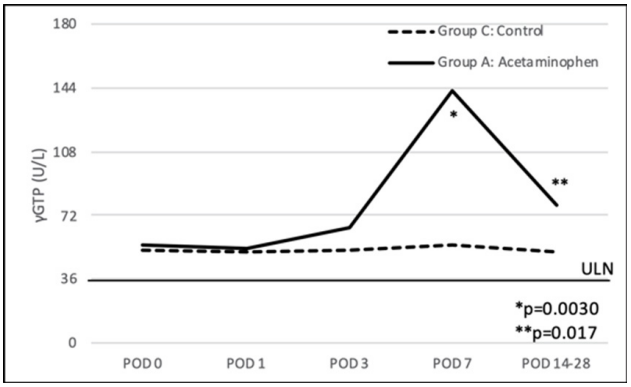
(c) ALT: ALT alanine aminotransferase, POD postoperative day.

In both groups, the ALT concentration was highest on POD 2 and then decreased gradually. The ALT concentrations did not differ significantly between groups.



(d) ALP: ALP alkaline phosphatase, POD postoperative day, ULN upper limit of normal.

The POD 7ALP concentration was significantly higher in Group A than in Group C, but all measured concentrations were below the upper limit of normal in both groups.



(e) γGTP: γGTP gamma-glutamyl transpeptidase, POD postoperative day, ULN upper limit of normal.

The POD 7 and POD 14–28 γGTP concentrations were significantly higher in Group A than in Group C.

In-hospital outcomes and postoperative complications

In-hospital outcomes and postoperative complications did not differ significantly between the two groups, as shown in Table 4. GI hypomotility lasted 2.6 days in Group C and 2.3 days in Group A. At least one dose of metoclopramide, reflective of PONV, was administered to 15 patients in Group C and 14 patients in Group A. Mean postoperative hospital stay was 12.7 days in Group C and 12.5 days in Group A. Postoperative hepatic failure (CTCAE ≥ Grade III) did not occur in either group. Postoperative complications of C-D grade ≤ II occurred in 1 (2.4%) of the 42 patients in Group C and in 2 (4.8%) of the 42 patients in Group A with no significant difference between the groups (p=0.557). No C-D grade ≥III postoperative complication occurred in either group. There was no in-hospital mortality.

		Group C (n=46)	Group A (n=46)	p Value
GI motility and PONV	Duration of intravenous infusion (days)	2.6 ± 0.4	2.3 ± 0.4	0.489
	Use of metoclopramide	15 (32.6%)	14 (30.4%)	1.000
	Postoperative hospital stay (days)	12.7 ± 1.0	12.5 ± 1.0	0.916
Morbidity	Hepatic failure (CTCAE Grade 3 or above)	0	0	1.000
Grade II		1	2	0.557
Grade III or above		0	0	1.000
Mortality		0	0	1.000

Table 4: In-hospital outcomes and postoperative complications, per group. Mean ± SE values, number of patients, or number (and percentage) of patients are shown, unless otherwise indicated.

Group C control group, Group A acetaminophen group, CTCAE Common Terminology Criteria for Adverse Events, GI gastrointestinal, PONV postoperative nausea and vomiting.

Discussion

Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways established to strengthened safety and help return patients to their normal activity level after major surgery by applying an evidence-based care strategy [7,8]. ERAS protocols are aimed at reducing surgical invasiveness, preventing surgical complications and promoting postoperative recovery. If successful, these protocols shorten the hospital stay and the time between surgery and the patient's return to normal life. For management of postoperative pain, multimodal pain control methods are recommended, including patient-controlled epidural analgesia [7,8].

Although combined use of a low-dose opioid and local anesthetic has been shown to be very effective, opioid use can suppress gastrointestinal (GI) motility and/or result in PONV [1,2]. An opioid-NSAID combination is effective after different types of

surgery because each of the two drugs has a different mechanism of action, with the opioid acting centrally on specific receptors and NSAID acting on the arachidonic acid cascade at peripheral sites [9,10]. Use of NSAIDs is not recommended, however, for patients with underlying liver disease and/or renal failure because of the possibility of aggravating the nephropathy and because of the risk of hemorrhage. Acetaminophen has become important in the management of postoperative pain, mainly because it seldom suppresses GI motility or causes PONV. As noted above, scheduled intravenous administration of acetaminophen has been shown to be useful for reducing the incidences of decreased GI motility and PONV following gastrectomy or esophageal surgery [1,2].

Acetaminophen is an antipyretic analgesic that is used worldwide because of its favorable safety profile and known clinical effectiveness. Since its release as an intravenous preparation in France, acetaminophen infusion has been used frequently for relief of postoperative pain. Clinical trials have shown the analgesic effect of acetaminophen to be superior to that of opioids, resulting in increased patient satisfaction, fewer complications and faster postoperative recovery [11,12]. In its Practice Guidelines for Acute Pain Management in the Perioperative Setting, the American Society of Anesthesiologists proposed multimodal analgesia. i.e., periodic administration of acetaminophen or an NSAID plus epidural anesthesia unless contraindicated [13].

However, NSAIDs are not given often when patients request them because of concerns over the possibility of aggravating an existing neuropathy, peptic ulcer or platelet dysfunction [10,14,15]. Acetaminophen is thought to have comparatively few side effects and is suitable for periodic administration because it inhibits prostaglandin only weakly. Acetaminophen is metabolized in the liver mainly via glucuronic acid conjugation, sulfate conjugation and oxidation, and it is excreted into the urine. When acetaminophen is administered in therapeutic doses, the metabolite N-Acetyl-4-benzoquinone imine (NAPQI) is inactivated by conjugation with glutathione. However, the glucuronic acid and sulfate pathways are saturated when acetaminophen is taken in in large doses, and NAPQI, which is a cytochrome P450 metabolite of acetaminophen, is generated and causes cytotoxicity. This hepatic cytotoxicity may be pronounced in elderly patients, in patients with alcoholic liver disease and in those who are malnourished [16]. Similarly, we expect the hepatic cytotoxicity to be amplified in patients after hepatectomy because of the unavoidable, ensuing decrease in liver function. Thus, we considered an investigation into the effect of periodic post-hepatectomy infusion of acetaminophen on liver function to be of utmost importance.

The appropriateness of periodic postoperative acetaminophen infusion has been reported in patients who have undergone surgeries other than hepatectomy [17-19]. Such administration has been shown to reduce postoperative pain. Researchers in Japan have shown that scheduled intravenous infusion of acetaminophen after esophagectomy decreases the incidence of PONV and that it may reduce postoperative opioid use [2]. Others in Japan have also shown that periodic infusion of acetaminophen added to thoracic epidural analgesia (TEA) provides postoperative pain management superior to that provided by TEA alone [1].

In the study described herein, we assessed a protocol we developed for post-hepatectomy pain management. The protocol involves periodic intravenous infusion of acetaminophen, and the drug regimen was shown to significantly decrease patients' need for infusion of the analgesic for the first 72 hours after hepatectomy. Epidural anesthesia was used for a significantly longer period by patients given acetaminophen periodically than by those given bolus doses of the NSAID, but it was used for more than 72 hours (on average) in both groups. Thus, we think periodic infusion of acetaminophen in addition to TEA provides better postoperative pain management than that provided by TEA alone. We note also that the acetaminophen regimen did not increase the incidence of severe postoperative complications. In addition, postoperative hepatic failure, a known adverse event related to acetaminophen use, did not occur.

Jahr and Lee indicated that acetaminophen is not subject to a first-pass effect [20], and others have shown that postoperative intravenous infusion of acetaminophen does not increase the incidence of postoperative hepatic complications [1,2,17–19,21,22]. However, there has not been a detailed report of postoperative change in markers of liver function. The serum TBL, AST, ALT and ALP concentrations changed similarly in our two study groups and returned to nearly normal levels by POD 14–28 at the latest. The serum γGTP concentration, however, was significantly high in our acetaminophen group on POD 7, and we regard this elevation to be a direct result of the periodic post-hepatectomy infusion of acetaminophen.

Our findings should be interpreted in light of the limitations of the study, including its execution as a retrospective clinical study that included historical controls and a relatively small number of patients. However, with the exception of postoperative pain management, the same postoperative care was given to patients in both groups. Therefore, the significant reduction in the use of analgesic agents for the first 72 hours after surgery and the serum γGTP elevation pointing to slight liver damage seem to be associated with our post-hepatectomy pain management strategy. Our results are encouraging and point to the need for a large-scale prospective study to confirm our findings.

Conclusion

Results of our study indicate that periodic intravenous infusion of acetaminophen after hepatectomy is a safe means of managing patients' postoperative pain.

Author Contributions

Conception and design of the study: M. Katayama, S. Koizumi; analysis and interpretation of the data: M. Katayama; collection and assembly of the data: all authors; drafting of the paper: M. Katayama, S. Koizumi; critical revision of the paper for important intellectual content: M. Katayama, S. Koizumi, S. Kobayashi, T. Otsubo; final approval of the paper: T. Otsubo.

Clinical Trial Registry

Institutional Review Board of St. Marianna University School of Medicine: Trial no. 4572.

UMIN Clinical Trials Registry: Trial no. UMIN000038600 (http://www.umin.ac.jp/ctr/index.htm).

Acknowledgments

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