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ORIGINAL ARTICLE

Antimicrobial prophylaxis for 1 day versus 3 days in liver cancer surgery: a randomized controlled non-inferiority trial

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Abstract

Purposes This study compared the effectiveness of 1-day vs 3-days antibiotic regimen to prevent surgical site infection (SSI) in open liver resection.

Method We performed a randomized controlled non-inferiority trial in 480 patients at 39 hospitals across Japan (registered as UMIN000002852). Patients with hepatocellular carcinoma scheduled to undergo resection were randomly assigned to receive either a 1-day regimen for antimicrobial prophylaxis, or a 3-day regimen. The primary endpoint was the incidence of SSI.

Results Among 480 randomized patients, 232 assigned to the 1-day regimen and 235 to the 3-day regimen were included in the full analysis set. Baseline characteristics of the two groups were well balanced. SSI was diagnosed in 22 patients (9.5%) in the 1-day group vs 23 patients (9.8%) in the 3-day group (difference, – 0.30; 90% CI – 4.80 to 4.19% [95% CI – 5.66% to 5.05%]; one-sided $P = 0.001$ for non-inferiority), meeting the non-inferiority hypothesis. In both groups, remote site infection (16 [6.9%] vs 22 [9.4%], $P < 0.001$ for non-inferiority) and drain-related infection (5 [2.2%] vs 4 [1.7%], $P < 0.001$ for non-inferiority) were comparable.

Conclusion To prevent SSI in liver cancer surgery, a 1-day regimen of flomoxef sodium is recommended for antimicrobial prophylaxis because of confirming the non-inferiority to longer usage.

Keywords Liver surgery · Hepatocellular carcinoma · Surgical site infection · Antimicrobial prophylaxis · Randomized controlled non-inferiority trial

Abbreviations

CDC	The Centers for Disease Control and Prevention
CI	Confidence interval
CT	Computed tomography
HCC	Hepatocellular carcinoma
MRI	Magnetic resonance imaging
SSI	Surgical site infection

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Introduction

Surgical site infection (SSI) remains the most crucial determinant of morbidity after surgery [1]. Since 1999 the Centers for Disease Control and Prevention (CDC) proposed guidelines for antimicrobial prophylaxis [2], and a number of studies on the prevention of SSI by prophylactic agents have been reported in several surgical categories [3, 4]. Moreover, CDC has updated in 2017 the guidelines to provide new evidence-based recommendations for the prevention of SSI [5].

Surgical antimicrobial prophylaxis aims to minimize the bacterial burden during operation that can be potentially diminished by host defense mechanisms [2] and is usually administered within 1 h before the incision, followed by supplementary injections every 3 or 4 h throughout the operation [3]. The CDC guidelines recommend that the prophylaxis should not be extended beyond 24 h after operation [2, 5], but the optimal duration remains controversial. In general practice, prophylactic agents have tended to be used for a longer duration than recommended [6, 7]. Nationwide cohort studies showed that surgeons continued postoperative prophylaxis for 2 or more days in 14% of North American patients and 27% of European patients [6] and for 3 or more days in 56% of Japanese patients [7], indicating that adherence to the guideline-oriented prophylaxis remains unsatisfactory worldwide. Therefore, the duration of administering antimicrobial prophylaxis is likely to depend on the surgeons' experience rather than concrete evidence.

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer-related mortality worldwide, and surgical strategies for safer resection will provide a chance for potential cure [8, 9]. Liver resection was classified as clean-contaminated surgery because the intrahepatic bile duct that would possess bacterial flora needs to be transected [2], and the incidences of SSI have been reported to be between 10.6 and 12.8% [10–15], which were higher than those in other categories [4]. After resection of HCC, antimicrobial prophylaxis tends to be used for longer than 5 days [13, 14], because background liver diseases are often linked to infectious events [11]. Although three randomized monocenter trials have assessed the optimum duration of prophylaxis in liver surgery, their clinical recommendations remain too weak to be generalizable mainly because of the design limitations [13–15]. In this context, our study is the first, multicenter, large randomized trial to compare a 1-day antimicrobial prophylaxis regimen with a 3-day regimen only in patients with HCC. We strictly defined the study protocol to evaluate the effectiveness of shorter usage of antibiotics, which is favored in an era of increasing adverse events, bacterial resistance, and health care costs [4]. On the assumption that the 1-day regimen would be noninferior to the longer regimen [14, 15], we calculated the sample size with an 8% noninferiority margin.

To elucidate the optimal duration of antimicrobial prophylaxis in liver cancer surgery, we conducted a non-inferiority randomized trial to compare the effectiveness of a 1-day regimen of flomoxef sodium for preventing SSI with that of a 3-day regimen.

Patients and methods

Trial design

This multicenter, open-label, non-inferiority, randomized controlled trial was conducted by the Surgical Site Infection Study Group of Japan, to compare the effectiveness of a 1-day regimen of flomoxef sodium vs that of a 3-day regimen for antimicrobial prophylaxis in liver cancer surgery. Patients were recruited between May 18, 2008 and September 30, 2010 at 39 university and the affiliated hospitals in Japan.

Flomoxef sodium was used as an antimicrobial prophylaxis agent in patients who underwent liver surgery [14, 15]. On the operation day, 1 g of flomoxef was administered 30 min before surgery, followed by 1 g every 3 h during surgery, and at 6 h after surgery [16]. Patients in the 3-day group additionally received 1 g of flomoxef every 12 h for 2 days after the operation. We selected flomoxef, a second-generation oxacephem agent, which exhibits potent antimicrobial activity against a variety of bacteria in the upper abdomen, causes fewer adverse events than other cephem agents, and has thus been widely used in patients undergoing clean-contaminated surgery such as hepatectomy [17].

The trial was performed in accordance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. The study protocol was approved by the steering committee of the Japan Society for Surgical Infection, as well as by the institutional review boards of all participating hospitals. All patients provided written informed consent before randomization. An English summary of the protocol is available on the Clinical Trials Registry managed by the University Hospital Medical Information Network in Japan (UMIN-CTR registration number: UMIN000002852), which can be accessed for free on the Internet (www.umin.ac.jp/ctr/index.htm).

Patients and Randomization

Patients who were scheduled to undergo elective resection for HCC associated with a specific imaging profile of tumor enhancement in the arterial phase and attenuation in the portal phase [18], diagnosed on computed tomography (CT) or magnetic resonance imaging (MRI) scan (or both) with no biopsy [19], were enrolled in this study. The clinical stage of HCC (Stage I–IV) was determined according to the Japanese General Rules for Primary Liver Cancer (3rd ed.) [20]. Participants had to meet the following inclusion criteria: three or less HCC of any size; liver function of Child–Pugh class A and indocyanine green retention rates of $<30\%$ at 15 min; a serum creatinine level of < 1.5mg/dL; and an age between 20 and 79 years.

Patients were excluded from the study if they underwent laparoscopic liver resection, concomitant with thoracotomy, concomitant radiofrequency ablation against HCC, reconstruction of the bile duct, or combined resection of organs other than the gallbladder. Patients with a past medical history of allergic reaction to flomoxef sodium, a serum urea nitrogen level of ˃25 mg/dL, or diabetes mellitus under insulin control, patients who had received corticosteroids, chemotherapy, or antibiotics within 2 weeks before surgery.

The enrolled patients were randomly allocated on a one-to-one basis via a central Web-based and password-protected service provided by BELSYSTEM24, Inc. (Harumi, Chuo-ku, Tokyo, Japan). Before surgery, patients who met the inclusion criteria were randomly assigned to the 1-day group or 3-day group by the stratified randomisation method in this open-label trial. The stratification factor was the hepatectomy procedure: major hepatectomy was defined as hemi-hepatectomy and bi-segmentectomies, and minor hepatectomy was defined as segmentectomy according to Couinaud's definition and limited resection [8, 21]. We used stratified block randomization with block size of four, independent across strata. The Randomized Clinical Trial Committee of the Japan Society for Surgical Infection was responsible for data management, central monitoring, and statistical analyses.

After central randomization, the surgeon was notified of the allocated intervention for the patients. Participants received the assigned treatment, but masking of the group assignment for the patients was not possible owing to logistical reasons. To ensure that the trial results were generally applicable, instructions on surgical indication and techniques in liver resection and postoperative management for the patients were not included in the protocol.

Study outcomes

The primary endpoint was the incidence of SSI after liver resection for HCC, and secondary endpoints included the incidences of infections at remote sites and those at the site around the surgical drain.

The incidence of infection was compared between the two groups within 30 days after operation. As a rule, infections were diagnosed when the culture test of the site suspected as being infected was positive. SSI was defined according to the Guidelines for the Prevention of SSI established by the CDC [2], which includes superficial, deep incisional, and organ/space SSI, and was diagnosed on the basis of the following findings: (1) inflammatory findings such as fever and flare, (2) drainage of pus from the incision or drain, (3) detection of pathogen by culture of fluid or tissue sample, and (4) fluid retention on enhanced CT indicating the presence of pus in a deep region. If postoperative infection was diagnosed during the study, the treatment was switched to therapeutic antimicrobial agents. Patients who were cases judged to have SSI clinically were also included in analysis, even if cultures were negative for pathogens.

Hematological and biochemical tests were performed before surgery and 1–7, 14, and 30 days after surgery, and bacteriological tests were performed as needed. Imaging examinations, such as chest radiography, abdominal ultrasonography, or CT, were performed as needed when postoperative infection was suspected. Bile leakage after liver resection was defined as a drain-fluid bilirubin level of higher than 5 mg/dL and for 3 days or longer [22].

A primary care team checked daily for the presence or absence of SSI during the hospital stay. After discharge, the principal surgeons checked for SSI in the outpatient clinics until 30 days after surgery. SSI was diagnosed made by the members of an independent adjudication committee, blinded to the patients' allocation, to guarantee the quality of evaluations in this study.

Statistical analyses

This study was based on the assumption that the 1-day regimen of antimicrobial prophylaxis would be noninferior to the 3-day regimen in terms of the primary efficacy endpoint. We calculated that a sample size of 410 patients in total would be required to provide a statistical power of 80%, based on an expected efficacy against the SSI incidence of the both regimens of 12% [10–12], a prespecified non-inferiority margin of 8%, and a one-sided type-I error of 0.05 (which was used because of the directional nature of the non-inferiority hypothesis). We planned to enroll 464 patients because a maximum possible loss of 10% of the patients was envisioned after their inclusion. The projected accrual period was 3 years, and no interim analysis was planned.

Analysis was done on an intention-to-treat basis with the full analysis set including all randomized patients who received at least one dose of antibiotic prophylaxis and were assessed for the primary and secondary endpoints [16].

A confirmatory analysis of the non-inferiority hypothesis was performed by providing the upper limit of the two-sided 90% confidence interval (CI), which corresponds to a one-sided test with a type-I error of 0.05, for the difference between the 1-day regimen minus the 3-day regimen in the incidence of SSI. If the upper limit of the CI would not exceed 8%, we would conclude that the non-inferiority of the 1-day regimen to the 3-day regimen was confirmed. As supportive information, a one-sided P value of the Dunnett–Gent test was provided for the non-inferiority hypothesis. As exploratory analyses, non-inferiority in terms of remote site infection and drain-related infection was also tested with a non-inferiority margin of 8% and presented with 95% CI for descriptive purpose. Differences in the categorical data between groups were analyzed by the Chi-square test. Continuous variables presented as medians (IQR) were compared using the Mann–Whitney U test. For variables except for the analyses of SSI, remote site infection, and drain-related infection, two-sided P values of less than 0.05 were considered to indicate statistical significance. Logistic regression analysis was done to adjust for potential confounding factors including age, sex, bilirubin, liver cancer stage, operation time, and blood loss. The patient subgroups were also analyzed with logistic regression to assess statistical interactions between the duration of antibiotics prophylaxis and the various subgroups.

Results

Study population

The 480 patients scheduled to undergo resection of HCC at 39 hospitals in Japan were enrolled and randomized; 240 were assigned to receive flomoxef sodium for 1 day, and 240 were to receive it for 3 days (Fig. 1). After randomization, 13 ineligible patients (8 in the 1-day group and 5 in the 3-day group) were excluded because they received no protocol prophylaxis and had no outcome data. Thus, 232 patients in the 1-day group and 235 patients in the 3-day group were included in the full analysis set. All patients received flomoxef according to the scheduled timing and doses and were monitored until 30 days after surgery.

The baseline characteristics of the two groups were well balanced (Table 1). The preoperative liver function and clinical stage of HCC were similar in both groups. The type of liver resection did not differ, and the between-group differences in the median operation time (14 min) and blood loss (88 mL) were minimal. A drainage tube was placed at the liver cut-stump in about 90% of the patients in each group, and postoperative bile leakage was positive in 5% or 7%, respectively.

Study outcomes

As for the primary outcome (Table 2), SSI was diagnosed in 22 (9.5%) of 232 patients in the 1-day group and 23 (9.8%) of 235 patients in the 3-day group (difference, – 0.30%; 90% CI, – 4.80% to 4.19%; [95% CI, – 5.66% to 5.05%]; one-sided $P = 0.001$ for non-inferiority by Dunnett–Gent test), thus meeting the prespecified level for non-inferiority. The most common SSI category was organ/space in each group, and 7 patients only in the 3-day group were found to simultaneously have two (5 patients) or three (2 patients) categories of SSI.

The interaction between the treatment effects of antibiotics regimens and six patient characteristics were assessed (Fig. S1), and no subgroups showed a decrease in the incidence of SSI with 3-day regimen.

The major pathogens among 10 bacteria identified in 45 patients with SSI were *Saureus* (7 patients) and *Sepidermidis* (4) in the 1-day group, and *Efaecalis* (5), *Saureus* (3) and coagulase-negative staphylococci (3) in the 3-day group, respectively (Table 3). Treatment for incisional SSI was opening the wound without or with irrigation, and those for organ/space SSI were the percutaneous drainage (8 in the 1-day group and 6 in the 3-day group), and the open drainage by re-operation because the abdominal abscess was massive (1 in the 3-day group).

In the 1-day and 3-day groups, remote site infection (16 patients [6.9%] vs 22 patients [9.4%]; difference, – 2.47%; 95% CI, – 7.42% to 2.48%; one-sided $P < 0.001$ for non-inferiority), and drain-related infection (5 [2.2%] vs 4 [1.7%]; 0.45%; 95% CI – 2.04% to 2.95%; one-sided $P < 0.001$ for non-inferiority) were comparable (Table 4).

Adverse events profiles did not differ between the groups (43 [18.5%] vs 36 [15.3%]; 3.22; 95% CI – 3.58 to 10.01; $P = 0.354$) (Table 5). No severe events occurred in either group, and no patient died within the trial follow-up period.

Fig. 1 CONSORT diagram

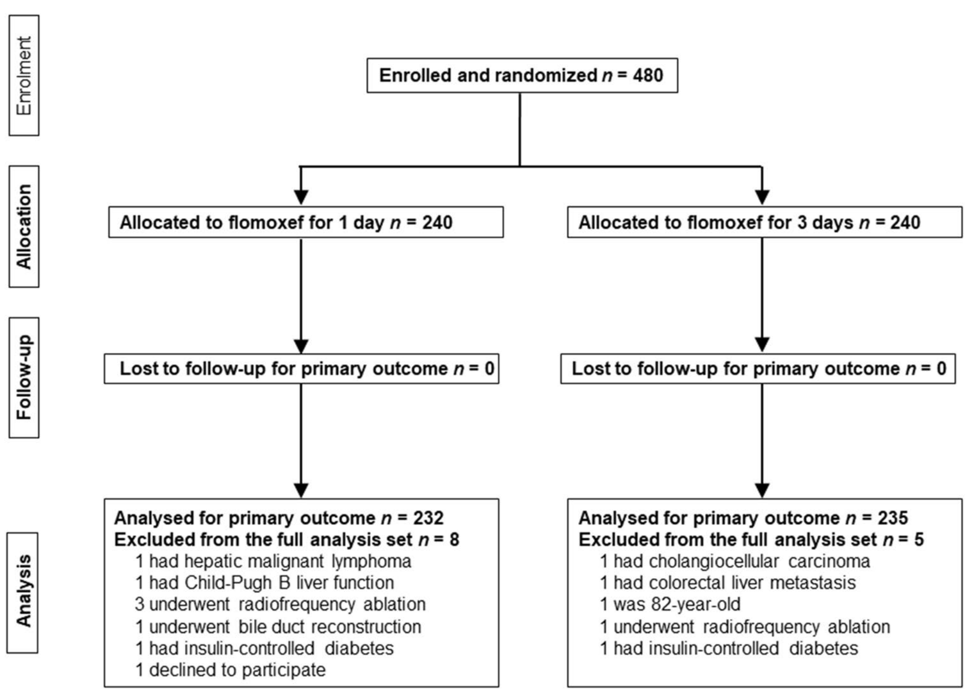

Table 1 Baseline and operative data

	Flomoxef for 1 day ($n=232$)	Flomoxef for 3 days ($n=235$)
Age, years	68 (62–73)	68 (60–73)
Men	191 (82%)	186 (79%)
Liver function		
Bilirubin, mg/dL	0.7 (0.5–1.0)	0.7 (0.5–1.0)
Alanine aminotransferase, IU/L	32 (22–49)	34 (23–57)
Aspartate aminotransferase, IU/L	35 (25–52)	35 (26–51)
Alkaline phosphatase, IU/L	265 (209–335)	266 (218–338)
Liver cancer stage[a]		
I	52 (23%)	48 (21%)
II	109 (47%)	95 (41%)
III	59 (26%)	70 (30%)
IV	10 (4%)	21 (9%)
Liver resection[b]		
Hemi-hepatectomy	37 (16%)	38 (16%)
Bi-segmentectomies	56 (24%)	59 (25%)
Segmentectomy	58 (25%)	64 (27%)
Limited resection	81 (35%)	74 (32%)
Operation time, min[c]	316 (230–382)	302 (224–406)
Blood loss, mL[d]	392 (174–775)	480 (185–970)
Blood transfusion	43 (19%)	51 (22%)
Drain tube, received	211 (91%)	205 (87%)
Bile leakage, positive[e]	11 (5%)	16 (7%)

Data are presented as the median (interquartile range) or number (%) of patients. No significant between-group differences were noted in any of the characteristics

[a]The stage was determined according to the Japanese General Rules for Primary Liver Cancer (3rd ed.), and data from two patients in the 1-day group and one patient in the 3-day group are missing

[b]Resection was classified as right or left hepatectomy, segmentectomy according to Couinaud's definition, and limited resection of less than one segment

[c]Data from two patients in the 1-day group and one patient in the 3-day group are missing

[d]Data from two patients in the 1-day group and two patients in the 3-day group are missing

[e]Leakage is defined as drain-fluid bilirubin ˃5 mg/dL for longer than 3 days

Discussion

In this randomized controlled trial, we confirmed that a 1-day regimen of flomoxef sodium was non-inferior to a 3-day regimen in terms of the incidence of SSI in patients undergoing resection of HCC. In addition, there were no between-group differences in the incidences of remote site infection, drain-related infection, or adverse events. To prevent SSI in liver cancer surgery, the 1-day regimen for antimicrobial prophylaxis can be highly recommended as the standard option of choice because it has been verified to be non-inferior to longer usage. This trial is the first in liver cancer surgery to provide robust evidence for the updated recommendation that antimicrobial prophylaxis should be discontinued within 24 h after operation [5, 23].

To date, three monocenter randomized trials have attempted to clarify the optimal usage of antimicrobial prophylaxis in liver cancer surgery, but these studies failed to provide useful clinical recommendations because of insufficient statistical power [13–15]. To overcome previous drawbacks, we planned to conduct a high-powered non-inferiority trial that fully met the CONSORT requirements. As compared with other studies, our randomized trial included several advantages in the predefined protocol, such as a uniform population (HCC patients alone), multicenter design (39 hospitals), larger sample size (2.6-fold) [15], extended hepatectomy (40%), and independent data management.

Our shortening of prophylaxis with flomoxef from 3 days to 1 day was not associated with an increased incidence of any SSI-related endpoint in patients who underwent surgery for HCC. The overall incidence of SSI in both groups was nearly equivalent (9.5% in the 1-day group and 9.8% in the 3-day group) and less than the median incidence (11.5%) in recent mega-cohort studies [10–12], which indicates that such a reduced duration of prophylaxis is optimal clinically. Others have reported that antibiotic usage for more than 3 days would induce bacterial resistance and increase the severity of infection [3, 4]. In fact, two or three categories of multiple SSIs were simultaneously diagnosed in seven patients only in the 3-day group. Moreover, we encountered one patient in the 3-day group who needed to undergo re-operation to drain an abdominal abscess at the surgical site of the liver (Clavien–Dindo grade IIIb) [9]. These findings are most likely attributable to resistance to flomoxef caused by longer usage, and the 1-day regimen might reduce such a risk of overlapping or severe infections. Secondary endpoints, such as remote site and drain-related infections, did not differ between the two groups. Infections were most commonly found in the respiratory tract (3.0% and 3.8%), and all cases were cured by optimal antimicrobial chemotherapy. The incidences of infections related to the surgical drains after hepatectomy were far lower (2.2% and 1.7%) than those (around 10%) reported in previous studies [24], which seems to be associated with the low incidences of bile leakage (5% and 7%) in our series. In all of the study endpoints assessed, these clear evidences suggested that our limited use of antimicrobial prophylaxis in liver surgery did not lead to any different clinical features between the two groups.

Recently, the updated Tokyo Guidelines have recommended that flomoxef sodium is a suitable prophylactic agent from a global perspective for controlling infections in the hepatobiliary system [17]. In this trial, we found a between-group difference in the strain of 10 bacteria identified in 45 patients who were diagnosed to have SSI (Table 3).

Table 2 Primary outcome

Outcome[a]	Flomoxef for 1 day ($n=232$)	Flomoxef for 3 days ($n=235$)	Difference% (90% CI)[b]	*P* value[c]
Surgical site infection	22 (9.5%)	23 (9.8%)	−0.30% (−4.80 to 4.19)	0.001
Superficial incisional	8 (3.4%)	11 (4.7%)		
Deep incisional	2 (0.9%)	5 (2.1%)		
Organ/space	12 (5.2%)	16 (6.8%)		

CI confidence interval

[a]Data are presented as numbers (%) of patients with at least one infection among three categories unless otherwise specified

[b]Non-inferiority of the 1-day regimen to the 3-day regimen was confirmed because the upper limit of the 90% CI does not exceed the predefined non-inferiority margin of 8%. In addition, the 95% CI for the between-group difference was "−5.66 to 5.05"

[c]One-sided P value for non-inferiority by the Dunnett–Gent test

Contact-borne bacteria such as *Saureus*, *Sepidermidis*, and coagulase-negative staphylococci were found in 12 of 22 patients in the 1-day group, and in 9 of 23 patients in the 3-day group, respectively. On the contrary, intestinal bacteria (less susceptible to flomoxef), such as *Efaecalis*, *Paerugi-nosa*, and *Smarcescens* were found in 7 patients only limited to the 3-day group, suggesting that the 'selection pressure' due to relatively longer prophylaxis is likely responsible for causing such enterobacterial SSI [3, 4]. As a microbiological consequence, the 1-day regimen of flomoxef will be recommended as a favorable option to reduce the risk of inducing antimicrobial resistance. In the culture results also showed that most of the bacteria in SSI were Gram-positive cocci and these were seen not only in the 3-day group but also in the 1-day group (Table 3), suggesting that Flomoxef prophylaxis might have an impact to select these bacteria. Even shortening the duration of treatment such as in the 1-day group might have these adverse effects.

Regarding the safety profile, the overall incidence of adverse events did not differ significantly between the two groups (18.5% in the 1-day group vs 15.3% in the 3-day group). No patient in either group had severe events, or discontinued the assigned regimen. Although shortening the duration of treatment did not reduce the incidence of adverse events, most events were mild in severity, and the incidences were consistent with those reported previously (15– 20%) [14, 15]. Hepatobiliary events were the most prevalent (81% and 83% of all events) and resolved within a week; these events were deemed unrelated to the study agent, but related to parenchymal transection of the liver because about 40% of the patients underwent major hepatectomies [25]. Hepatectomy-related events, such as thrombi in the portal vein (1 patient per group) and intervention-related bleeding (3 patients in the 1-day group), were cured with no need for re-operation, but the possible causes remain unknown. No patient with bleeding tendency related to flomoxef was identified during or after hepatectomy in both groups. Notably, we achieved 'zero mortality' in hepatectomy for all of the 467 patients at 39 hospitals in Japan, where the operative mortality rate is approximately 1% [26].

Factors related to the incidence of SSI in liver surgery have been reported to include age, bilirubin, liver cancer stage, hepatectomy procedure, operation time, and blood loss [11, 27], all of which were well balanced between the groups in our study. In this trial, the surgeons successfully performed hepatectomy with good performance, such as a small median blood loss (392 mL vs 480 mL), low transfusion rate (19% vs 22%), and low bile leak rate (5% vs 7%). In addition, logistic regression analyses with adjustment for 6 factors (as mentioned above) indicated that no subgroups would favor to recommend the 3-day regimen with respect to the incidence of SSI.

In this study, the type of hepatectomy was used as the stratification variable, not the length of incision or type of incision because of following reasons. First, unlike previous studies, because this study is a multicenter design, it was expected that patients with various incisions were mixed. Second, the length of the incision is considered to be correlated with the size of the resected specimen, that is, the hepatectomy procedure, and one of the factors related to the incidence of SSI in liver surgery have been reported hepatectomy procedure [11, 27]. Finally, to date, three monocenter randomized trials have attempted to clarify the optimal usage of antimicrobial prophylaxis in liver cancer surgery, but these studies did not use the length of incision as the stratification variable [13–15].

The design of our randomized trial may raise some concerns. First, the antimicrobial prophylactic agent was added once after closure of skin incision [16]. At the time of making this protocol, the present concept of restrictive use of postoperative prophylaxis was not fully evidenced especially in liver surgery [13, 14], and blood loss during liver resection would be expected to be massive (around 1000 mL) in about 40% of the patients [13–15], which obliged us to give 1 g of antibiotics 6 h after surgery as a supplement [2, 3]. Second, we first adopted the multicenter design to clarify

Table 3 Bacteria and treatment

	Flomoxef for 1 day	Flomoxef for 3 days
Bacteria[a]		
Superficial incisional	(*n* = 8)	(*n* = 11)
Methicillin-resistant *Staphylococcus aureus*	2	0
Staphylococcus epidermidis	1	0
Coagulase-negative staphylococci	1	3
Enterococcus faecalis	0	1
Pseudomonas aeruginosa	0	1
Unknown	4	7
Deep incisional	(*n* = 2)	(*n* = 5)
Staphylococcus epidermidis	2	1
Acinetobacter spp.	1	0
Methicillin-resistant *Staphylococcus aureus*	0	1
Enterococcus faecalis	0	1
Unknown	0	3
Organ/space	(*n* = 12)	(*n* = 16)
Staphylococcus aureus	3	2
Methicillin-resistant *Staphylococcus aureus*	2	2
Staphylococcus epidermidis	1	0
Klebsiella oxytoca	1	0
Enterococcus faecalis	0	3
Serratia marcescens	0	1
Corynebacterium spp.	0	1
Unknown	5	7
Treatment[b]		
Superficial incisional	(*n* = 8)	(*n* = 11)
Opening the wound	8	11
Deep incisional	(*n* = 2)	(n = 5)
Opening the wound with irrigation	2	5
Organ/space	(*n* = 12)	(*n* = 16)
Antimicrobial escalation/adjustment	5	10
Percutaneous drainage	8	6
Laparotomized drainage	0	1

Data are present as the number of patients

[a]The bacteria identified in the 1-day group were methicillin-resistant *Staphylococcusaureus* (*n* = 4), *Staphylococcusepidermidis* (4), *Staphylococcusaureus* (3), others (3) and unknown (9), and those in the 3-day group were *Enterococcusfaecalis* (5), methicillin-resistant *Staphylococcusaureus* (3), coagulase-negative staphylococci (3), others (6) and unknown (17)

[b]Treatment for organ/space infection included percutaneous drainage in eight patients in the 1-day group and in six patients in the 3-day group, and laparotomized drainage (Clavien–Dindo IIIB) in one patient in the 3-day group

whether the marginally positive results obtained in a single hospital would be statistically true [13–15]. Because mono-center trials have the risk of overestimating treatment effects [28], we included 39 hospitals in this trial to strength the generalizability of our results. Third, a non-inferiority margin was selected arbitrarily, and a margin of 10% has been used practically to compare the efficacy of antibiotics [16]. We decided to use an 8% margin in our study, but the upper limit of the 90% CI (4.19%) in this trial indicates that the non-inferiority of the 1-day prophylaxis can be guaranteed to meet the prespecified hypothesis, which has been reassured even by the application of 95% CI (5.05%) to this setting. Finally, the limitation whereby this trial was designed as 'open-label' probably did not greatly affect the evaluation of comparative efficacy. To avoid underestimation of the incidence of SSI, this study required the principal surgeons in the primary care team to check daily for the presence or absence of SSI until 30 days after surgery [3]. Moreover, the assessment of SSI was done by independent surgeons in the adjudication team who were masked to the duration

Table 4 Secondary outcomes

Outcomes[a]	Flomoxef for 1 day ($n=232$)	Flomoxef for 3 days ($n=235$)	Difference % (95% CI)	*P* value[b]
Remote site infection[c]	16 (6.9%)	22 (9.4%)	−2.47% (−7.42 to 2.48)	<0.001
Respiratory tract	7 (3.0%)	9 (3.8%)		
Device infection	5 (2.2%)	6 (2.6%)		
Biliary tract	1 (0.4%)	2 (0.9%)		
Enterocolitis	1 (0.4%)	2 (0.9%)		
Sepsis	1 (0.4%)	2 (0.9%)		
Urinary tract	1 (0.4%)	0 (0.0%)		
Others	4 (1.7%)	3 (1.3%)		
Drain-related infection[d]	5 (2.2%)	4 (1.7%)	0.45% (−2.04 to 2.95)	<0.001
POD 1–7	3 (1.3%)	3 (1.3%)		
POD 8–14	2 (0.9%)	1 (0.4%)		

POD postoperative day, *CI* confidence interval

[a]Data are presented as numbers (%) of patients with at least one remote site infection or drain-related infection unless otherwise specified

[b]One-sided p value for non-inferiority by the Dunnett–Gent test

[c]The bacteria identified in the 1-day group were *Staphylococcus* spp. ($n=6$), *Pseudomonasaeruginosa* (2), others (4) and unknown (9), and those in the 3-day group were *Staphylococcus* spp. (4) and *Enterococcusfaecalis* (2), others (5) and unknown (8)

[d]The bacteria identified in the 1-day group were *Staphylococcusaureus* (3), *Enterococcus* spp. (1) and unknown (1), and those in the 3-day group were *Pseudomonasaeruginosa* (2), *Staphylococcusepidermidis* (1) and *Streptococcushemolyticus* (1)

Table 5 Adverse events

Events[a]	Flomoxef for 1 day ($n=232$)	Flomoxef for 3 days ($n=235$)	Difference % (95% CI)	*P* value[b]
Total	43 (18.5%)	36 (15.3%)	3.22% (−3.58 to 10.01)	0.354
Hepatobiliary[c]	35 (15.1%)	30 (12.8%)		
Renal[d]	7 (3.0%)	3 (1.3%)		
Metabolic[e]	3 (1.3%)	3 (1.3%)		
Digestive[f]	2 (0.9%)	4 (1.7%)		
Intervention[g]	3 (1.3%)	0		
Cardiorespiratory	1 (0.4%)	2 (0.9%)		
Peritonitis	1 (0.4%)	2 (0.9%)		
Neurological	0	1 (0.4%)		
Dermal	1 (0.4%)	0		
Others	2 (0.9%)	1 (0.4%)		
Death	0	0		

BUN blood urea nitrogen, *CI* confidence interval

[a]Data are presented as numbers (%) of patients with at least one event unless otherwise specified

[b]Two-sided *P* value by the Chi-square test

[c]Postoperative increases in AST and ALT that met Hy's law criteria were observed (34 patients in the 1-day group and 29 in the 3-day group) and resolved within a week. Thrombi in the portal vein were diagnosed by ultrasonography in 1 patient in each group and disappeared with the continuous injection of heparin

[d]Elevation of BUN was seen (six patients in the 1-day group and three in the 3-day group) but normalized within 3 days, and one patient in the 1-day group had oliguria for 3 days

[e]Electrolyte imbalance was evident (three patients in each group) but returned to normal within 5 days with optimal hydration

[f]Nausea in two patients occurred in the 1-day group, and ascites in two patients and colitis in two patients occurred in the 3-day group

[g]When draining fluid collection, a small amount of bleeding was detected in three patients in the 1-day group, but this was resolved with no need for re-operation

of prophylaxis. Thus, the drawback of being open-labeled probably did not bias the comparison of the SSI incidence between the two groups.

Conclusion

Our findings clarify robust evidence that 1 day of antimicrobial prophylaxis with flomoxef sodium is noninferior to 3 days of prophylaxis and has a good safety profile when used to prevent SSI in patients undergoing resection of HCC. To improve the risk–benefit ratio of prophylaxis, use of the 1-day regimen can provide benefits for patients by potentially reducing the risks of antibiotic-related adverse events, bacterial resistance, and medical costs. This trial is the first in liver cancer surgery to provide the clinical foundation of the recommendations to prevent SSI in the updated guidelines [5, 23].

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Compliance with ethical standards

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References

1. Burke JP. Infection control—a problem for patient safety. N Engl J Med. 2003;348(7):651–6.
2. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27(2):97–132.
3. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA, American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70(3):195–283.
4. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. Lancet Infect Dis. 2015;15(12):1429–37.
5. Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP, Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152(8):784–91.
6. Alexiou VG, Ierodiakonou V, Peppas G, Falagas ME. Antimicrobial prophylaxis in surgery: an international survey. Surg Infect (Larchmt). 2010;11(4):343–8.
7. Imamura H, Kurokawa Y, Tsujinaka T, Inoue K, Kimura Y, Iijima S, et al. Intraoperative versus extended antimicrobial prophylaxis after gastric cancer surgery: a phase 3, open-label, randomised controlled, non-inferiority trial. Lancet Infect Dis. 2012;12(5):381–7.
8. Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet. 2000;356(9232):802–7.
9. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med. 2007;356(15):1545–59.

10. Moreno Elola-Olaso A, Davenport DL, Hundley JC, Daily MF, Gedaly R. Predictors of surgical site infection after liver resection: a multicentre analysis using National Surgical Quality Improvement Program data. HPB (Oxford). 2012;14(2):136–41.
11. Nakahira S, Shimizu J, Miyamoto A, Kobayashi S, Umeshita K, Ito T, et al. Proposal for a sub-classification of hepato-biliary-pancreatic operations for surgical site infection surveillance following assessment of results of prospective multicenter data. J Hepatobiliary Pancreat Sci. 2013;20(5):504–11.
12. Paruch JL, Merkow RP, Bentrem DJ, Ko CY, Posner MC, Cohen ME, et al. Impact of hepatectomy surgical complexity on outcomes and hospital quality rankings. Ann Surg Oncol. 2014;21(6):1773–800.
13. Wu CC, Yeh DC, Lin MC, Liu TJ, Peng FK. Prospective randomized trial of systemic antibiotics in patients undergoing liver resection. Br J Surg. 1998;85(4):489–93.
14. Togo S, Tanaka K, Matsuo K, Nagano Y, Ueda M, Morioka D, Endo I, Shimada H. Duration of antimicrobial prophylaxis in patients undergoing hepatectomy: a prospective randomized controlled trial using flomoxef. J Antimicrob Chemother. 2007;59(5):964–70.
15. Hirokawa F, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, et al. Evaluation of postoperative antibiotic prophylaxis after liver resection: a randomized controlled trial. Am J Surg. 2013;206(1):8–15.
16. Takagane A, Mohri Y, Konishi T, Fukushima R, Noie T, Sueyoshi S, et al. Randomized clinical trial of 24 versus 72 h antimicrobial prophylaxis in patients undergoing open total gastrectomy for gastric cancer. Br J Surg. 2017;104(2):e158–e164164.
17. Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, Kusachi S, Mayumi T, Miura F, Kiriyama S, Yokoe M, Kimura Y, Higuchi R, Windsor JA, Dervenis C, Liau KH, Kim MH, Tokyo Guideline Revision Committee. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20(1):60–70.
18. Midorikawa Y, Takayama T, Nara S, Hashimoto T, Omichi K, Ebisawa K, et al. No Need of Immediate Treatment for Hypovascular Tumors Associated with Hepatocellular Carcinoma. World J Surg. 2016;40(10):2460–5.
19. Levy I, Greig PD, Gallinger S, Langer B, Sherman M. Resection of hepatocellular carcinoma without preoperative tumor biopsy. Ann Surg. 2001;234(2):206–9.
20. Liver Cancer Study Group of Japan. The clinical staging of hepatocellular carcinoma. In: Makuuchi M, editor. General rules for the clinical and pathological study of primary liver cancer. 3rd ed. Ltd, Tokyo: Kanehara & Co.; 2010. p. 26–27.
21. Takayama T, Makuuchi M, Kubota K, Harihara Y, Hui AM, Sano K, et al. Randomized comparison of ultrasonic vs clamp transection of the liver. Arch Surg. 2001;136(8):922–8.
22. Yamazaki S, Takayama T, Moriguchi M, Mitsuka Y, Okada S, Midorikawa Y, et al. Criteria for drain removal following liver resection. Br J Surg. 2012;99(11):1584–90.
23. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, Itani KM, Dellinger EP, Ko CY, Duane TM. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. J Am Coll Surg. 2017;224(1):59–74.
24. Liu CL, Fan ST, Lo CM, Wong Y, Ng IO, Lam CM, et al. Abdominal drainage after hepatic resection is contraindicated in patients with chronic liver diseases. Ann Surg. 2004;239(2):194–201.
25. Pelton JJ, Hoffman JP, Eisenberg BL. Comparison of liver function tests after hepatic lobectomy and hepatic wedge resection. Am Surg. 1998;64(5):408–14.
26. Kudo M, Izumi N, Ichida T, Ku Y, Kokudo N, Sakamoto M, et al. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res. 2016;46(5):372–90.
27. Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg. 2003;237(4):536–43.
28. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med. 2011;155(1):39–51.

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