—Original—

Investigation of the Optimal Interval of Perioperative Serum Flomoxef Administration in Hepatobiliary-Pancreatic Surgery

Yoko Takayama[1,2], Toshiaki Komatsu[3], Satomi Tsumuraya[4], Hidefumi Kubo[5], Nobuyuki Nishizawa[5], Hiroshi Tajima[5], Takashi Kaizu[5], Katsuya Otori[6], Hirotsugu Okamoto[7], Yusuke Kumamoto[5] and Hideaki Hanaki[8]

[1]Department of Infection Control and Infectious Diseases, Research and Development Center for New Medical Frontiers, Kitasato University School of Medicine, Kanagawa, Japan
[2]Department of Infection Control and Prevention, Kitasato University Hospital, Kanagawa, Japan
[3]Department of Pharmacy, Kitasato University Hospital, Kanagawa, Japan
[4]Sogo Medical Company Limited, Tokyo, Japan
[5]Department of General-Pediatric-Hepatobiliary Pancreatic Surgery, Kitasato University School of Medicine, Kanagawa, Japan
[6]Pharmacy Practice and Science I, Research and Education Center for Clinical Pharmacy, Kitasato University School of Pharmacy, Tokyo, Japan
[7]Department of Anesthesiology, Kitasato University School of Medicine, Kanagawa, Japan
[8]Infection Control Research Center, The Omura Satoshi Memorial Institution, Kitasato University, Tokyo, Japan

Background: Perioperative prophylactic antimicrobials are re-administered at intervals of twice their half-life. However, the actual concentrations of antimicrobial agents and the degree of elevation remain unelucidated.

Methods: This prospective cohort study was conducted at a single tertiary care center. Serum concentrations were evaluated in patients who underwent hepatobiliary-pancreatic surgery between April 2019 and December 2020 and received an additional dose of flomoxef (FMOX) every 3 h or 5 h during the surgical procedure based on their renal function.

Results: Among the 31 participants, 25 and six received FMOX every 3 h and 5 h, respectively. Analysis based on renal function revealed median FMOX concentrations of 9.88 mg/L and 9.85 mg/L ($p = 0.09$) for patients with creatinine clearance (Ccr) >60 mL/min and 14.26 mg/L and 20.03 mg/L ($p = 0.02$) for the patients with Ccr ≤60 mL/min at 3 h and 6 h, respectively, with notable elevation at Ccr ≤60 mL/min. Moreover, the serum FMOX concentration at 6 h for the 3-h dosing patients with Ccr ≤60 mL/min was significantly higher than the concentration at 5 h for the 5-h dosing patients with Ccr ≤60 mL/min (20.03 mg/L vs. 12.85 mg/L, $p = 0.04$). Although serum concentrations at 3-h and 6-h intervals did not differ significantly in patients with Ccr ≥60 mL/min, these significantly increased in patients with Ccr <60 mL/min.

Conclusions: Administering FMOX every 3 h when Ccr is ≥60 mL/min and every 5 h when Ccr is <60 mL/min are appropriate. (J Nippon Med Sch 2025; 92: 196–203)

Key words: serum concentration, flomoxef, dosing interval, renal function, hepatobiliary-pancreatic surgery

Introduction

Flomoxef (FMOX; oxacephem), a β-lactam antibiotic with broad-spectrum antibacterial activity against gram-positive and gram-negative aerobic and anaerobic bacteria[1], is approved for use in Japan, China, Korea, and Taiwan[2]. Globally, with the continued increase in the num-

Correspondence to Yoko Takayama, Department of Infection Control and Infectious Diseases, Research and Development Center for New Medical Frontiers, Kitasato University School of Medicine, 1–15–1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252–0374, Japan
E-mail: yoko@med.kitasato-u.ac.jp
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ber of affected patients, infections by extended-spectrum beta-lactamase (ESBL)-producing bacteria are a significant threat[3–5]. FMOX may have a comparable therapeutic efficacy as that of carbapenem against ESBL-producing *Enterobacteriaceae* infections[6–8] and can be a substitute antimicrobial to carbapenems. The antibacterial and therapeutic effects of FMOX correlate with the duration of exposure, wherein the concentrations, particularly at the site of action, remain above the minimum inhibitory concentration (MIC) required for inhibiting bacterial growth (T > MIC)[2,9,10]. FMOX has a wide range of therapeutic indications, including pneumonia, urinary tract infections, and abdominal infections, and is a prophylactic antibiotic in hepatobiliary-pancreatic surgery[11].

For antimicrobial prophylaxis to prevent surgical site infections (SSIs), it is imperative to achieve and maintain adequate antibiotic concentrations near the surgical site[12–14]. In cases of prolonged surgeries (i.e., those extending beyond two half-lives of the drug after the initial dose), intraoperative antibiotic administration is required to ensure adequate antimicrobial concentration until the surgery is completed[15,16]. In Japan, FMOX is administered 30 min preoperatively, with subsequent intraoperative redosing every 3 h, according to FMOX's twice-half-life dosing regimen[15,17,18]. This administration interval may be extended for patients with renal dysfunction[19]. Multi-dose FMOX administration for antimicrobial prophylaxis during the perioperative period is recommended for neurosurgery ≥6 h in patients without renal dysfunction[20].

The guidelines from the United States Centers for Disease Control and Prevention (CDC) recommend that the administration of preoperative antimicrobial prophylaxis should follow the confirmation of bactericidal antimicrobial concentrations in the serum and tissue at the time of the first incision[21]. However, the actual FMOX concentration and elevation have not been comprehensively examined. This study aimed to verify whether the current dosing regimen adequately maintains the required FMOX concentration.

Material and Methods

Design, Setting, and Patients

This prospective cohort study was conducted using data obtained from 31 patients who received treatment at Kitasato University Hospital, Kanagawa, Japan. These patients provided their consent to undergo laparoscopy (23 patients) or laparotomy (eight patients) during hepatobiliary-pancreatic surgery and received FMOX as a perioperative prophylactic antimicrobial between April 2019 and December 2020. FMOX was administered every 3 h or 5 h when creatinine clearance (Ccr) was >60 and ≤60 mL/min, respectively[22,23]. Patients allergic to FMOX, aged <20 years, pregnant, or breastfeeding were excluded.

Sample Collection

All 31 patients were administered 1 g FMOX intravenously within 10 min following anesthesia induction and within 60 min before the surgical incision. Blood samples were collected at the time of redosing and promptly centrifuged at 1,610 × *g* for 10 min. The resulting serum samples were stored at −30°C until further analysis.

Determination of Serum FMOX Concentrations

Serum FMOX concentration was measured using high-performance liquid chromatography, as described previously[11]. The serum samples (200 µL) were mixed with 90 µL of a deproteinizing agent (1 M $HClO_4$) and centrifuged at 10,000 × *g* for 10 min. A sample solution (50 µL) was then injected into a C18 column maintained at 10°C. The mobile phase consisted of 70% 50 mM phosphate buffer (pH 4.5), 28% methanol, and 2% tetrahydrofuran. The samples were separated in the mobile phase at a flow rate of 0.8 mL/min, and the eluate was monitored at 272 nm using an ultraviolet absorption detector.

Evaluation of SSIs

Wound infections were identified in accordance with the guidelines of the United States CDC/National Healthcare Safety Network[24]. Postoperatively, the patients were followed up daily during their hospital stay by a trained physician and monitored weekly in the outpatient clinic for up to 30 days. The following risk factors for SSIs in hepatobiliary-pancreatic surgery were investigated: male sex, body mass index ≥30 kg/m^2, bilirubin ≥2.0 mg/dL, American Society of Anesthesiologists (ASA) classification of ≥3, open surgery, prolonged surgery (defined as a surgery longer than the 75th percentile of surgery duration as reported by the Japanese Healthcare-Associated Infections Surveillance), and perioperative blood transfusion >75th percentile[25,26]. Moreover, according to previous studies, the risk factors for pancreas-specific SSIs, preoperative biliary drainage, chemotherapy, and radiotherapy, and liver-specific SSIs, smoking, albumin <3.5 g/dL, and significant blood loss, were evaluated[25,26].

The MIC_{90} values for methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Escherichia coli* were set at 0.5 and 1 mg/L, respectively[27].

Statistical Analyses

Descriptive data were expressed as median and inter-

Table 1 Patient characteristics

Factors	Number	Median (IQR)	Range
Patients (male/female)	21/10		
Age (years)		69 (63–74)	35–87
Body weight (kg)		61.6 (54.2–68.3)	42.9–74.6
Body mass index (kg/m²)		22.8 (21.3–24.8)	17.8–45.3
Ccr* (mL/min)		68 (51–83)	32–143
Laparoscopic surgery	23		
FMOX additional doses every 3 h	19	3 h: 10.58 (8.56–13.99)	4.25–25.68
		6 h: 11.95 (9.51–16.28)	5.15–33.51
Laparotomic surgery	8		
FMOX additional doses every 3 h	6	3 h: 9.67 (7.67–11.44)	5.89–18.60
		6 h: 9.76 (7.06–11.17)	5.28–20.66
Blood loss (mL)		234 (119–520)	0–10,692
Operative time (min)		469 (418–586)	334–788
Preoperative transfusion	1		

FMOX: flomoxef, Ccr: creatinine clearance, IQR: interquartile range
*Estimated by the Cockcroft-Gault equation

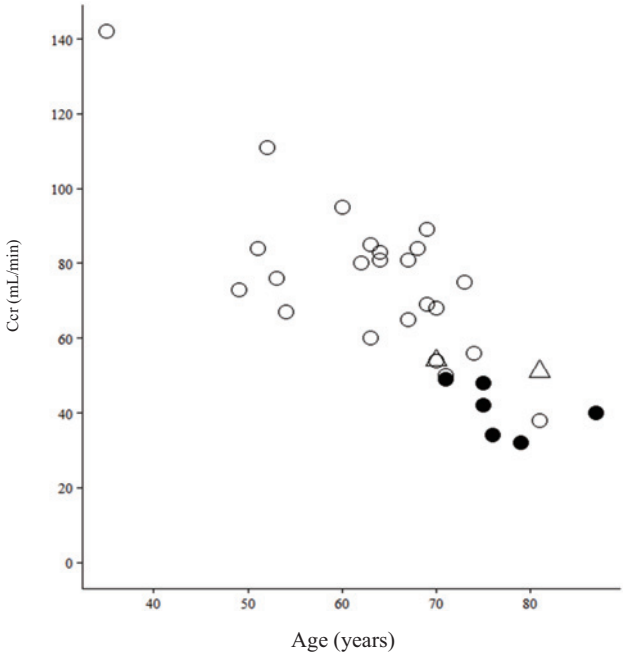

Fig. 1 Relationship between age and renal function
○: 3 h after FMOX administration; N=25, ●: 5 h after FMOX administration; N=6, △: 3 h after FMOX administration (cases of surgical site infections), Ccr: creatinine clearance

quartile range (IQR). The Wilcoxon signed-rank sum test was used to analyze the data at 3 h and 6 h timepoints post-FMOX administration. Other parametric data were analyzed using the Mann-Whitney U test. The survey results of all cases were statistically analyzed using JMP software (version 14.0; SAS Institute Japan Co., Ltd, Tokyo, Japan).

Ethics Approval

This study was approved by the Ethics Committee of Kitasato University Hospital (approval number: B16-277) and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent for the publication of this report was obtained from all patients.

Results

Clinical Features of the Patients

The characteristics of the patients are presented in **Table 1**. Underlying diseases included metastatic liver cancer (nine patients), hepatic cell carcinoma (seven patients), pancreatic cancer (four patients), papillary mucinous tumor in the pancreatic duct (four patients), cholangiocarcinoma (three patients), and others (four patients: one each of hepatocellular adenoma, xanthogranuloma cholecystitis, perivascular epithelioid tumor, and hepatic vascular tumor). The relationship between age and renal function is shown in **Figure 1**. The renal function of the two SSI cases was Ccr 51.74 mL/min for Case 1 and Ccr 54.33 mL/min for Case 2.

Risk Factors of SSIs

Two of the 31 patients (6.5%) experienced SSIs. The risk factor in Case 1 (hepatic cell carcinoma) was an operative time of 662 min, whereas those in Case 2 (papillary mucinous tumor in the pancreatic duct) were an operative time of 469 min, ASA of 3, and male sex. The 29 patients with no SSIs had 0 to 3 risk factors, respectively, which did not differ from those of patients with SSIs (data not shown).

Comparison of Serum FMOX Concentrations

FMOX was administered every 3 h (at 3 h, 6 h, and 9 h) in 25 patients (**Fig. 2**) and every 5 h in six patients. Among the 25 patients, 18 had a Ccr of >60 mL/min and seven had a Ccr of ≤60 mL/min. The median serum FMOX concentration for the group receiving FMOX every 3 h was 10.58 mg/L at 3 h and 11.21 mg/L at 6 h, indicating an elevation of concentration at 6 h ($p < 0.01$). Furthermore, analysis based on renal function revealed median FMOX concentrations of 9.88 mg/L and 9.85 mg/L ($p = 0.09$) for the patients with Ccr >60 mL/min and 14.26 mg/L and 20.03 mg/L ($p = 0.02$) for the patients with Ccr ≤60 mL/min at 3 h and 6 h, respectively, with notable elevation at Ccr ≤60 mL/min (**Table 2**). All patients who received the medication every 5 h had a Ccr of ≤60 mL/min. The serum FMOX concentrations at 3 h for the 3-h dosing patients with Ccr >60 mL/min (9.88 mg/L) and Ccr ≤60 mL/min (14.26 mg/L) showed no significant difference with concentrations at 5 h for the 5-h dosing patients (12.85 mg/L) (**Fig. 3A and B**). Similarly, the serum FMOX concentration at 6 h for the 3-h dosing patients with Ccr >60 mL/min was not significantly different from the concentration at 5 h for the 5-h dosing patients with Ccr >60 mL/min (9.85 mg/L and 12.85 mg/L, respectively) (**Fig. 4A**). However, the FMOX concentration at 6 h for the 3-h dosing patients with Ccr ≤60 mL/min was significantly higher than the concentration at 5 h for the 5-h dosing patients with Ccr ≤60 mL/min (20.03 mg/L vs. 12.85 mg/L, $p = 0.04$) (**Fig. 4B**).

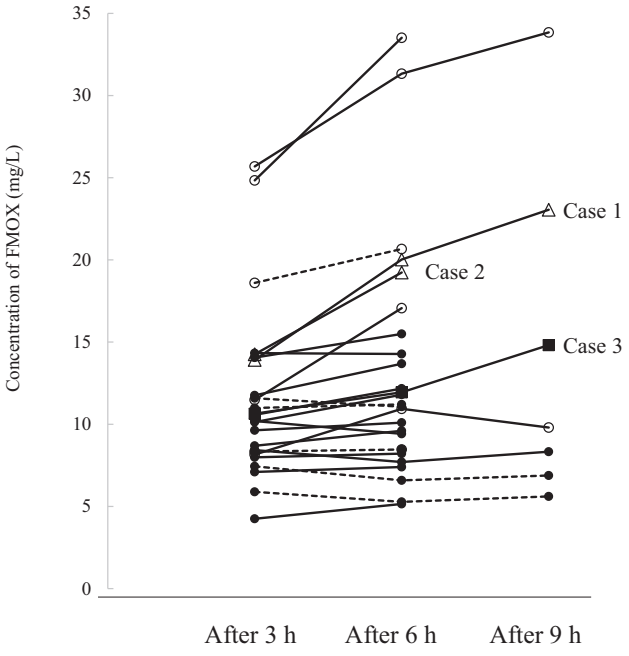

Fig. 2 Comparison of serum median FMOX concentrations at 3, 6, and 9 h after administration
●: Ccr >60 mL/min, ○: Ccr ≤60 mL/min, ------: laparotomic surgery, ——: laparoscopic surgery, △: cases of surgical site infections (Ccr ≤60 mL/min), ■: case with 10,692 mL of blood loss (Ccr >60 mL/min), FMOX: flomoxef, Ccr: creatinine clearance

Differences in serum FMOX concentrations between laparoscopy and laparotomy were also investigated, but no significant differences were observed (**Table 1**). The number of patients who received FMOX every 5 h was small (four laparoscopies and two laparotomies), which hindered statistical analysis. The 3 h serum median concentration of FMOX was 14.09 mg/L in two patients with SSIs and 10.19 mg/L in 29 patients without SSIs. The 6 h serum median concentration of FMOX was 19.43 mg/L in the SSI cases and 11.06 mg/L in the non-SSI cases. No significant differences in serum FMOX concentration were observed between the SSI and non-SSI groups.

Discussion

To the best of our knowledge, this is the first report to determine and evaluate the actual serum FMOX concentrations, including the presence of SSIs. In patients with Ccr ≤60 mL/min, a comparison of FMOX concentrations at 6 h and 5 h after administration showed a predominant elevation of FMOX at 6 h (**Fig. 4B**). Therefore, FMOX administration every 5 h for patients with Ccr ≤60 mL/min was deemed suitable. Our results indicated that in patients with Ccr >60 mL/min, there was no elevation of FMOX when administered every 3 h (**Fig. 3A, 4 A**), suggesting that the administration interval was indeed appropriate. This judicious use of antimicrobial agents may facilitate the effective management of drug-

Table 2 Comparison of serum FMOX concentrations at 3 and 6 h after additional dose administration

Renal function	3 h after dosing (mg/L) median (IQR)	6 h after dosing (mg/L) median (IQR)	*P*
All cases (N=25)	10.58 (8.34–13.91)	11.21 (8.46–15.49)	<0.01
Ccr >60 mL/min (N=18)	9.88 (8.08–10.90)	9.85 (7.83–11.91)	0.09
Ccr ≤60 mL/min (N=7)	14.26 (12.70–21.72)	20.03 (18.15–26.00)	0.02

FMOX: flomoxef, IQR: interquartile range, Ccr: creatinine clearance

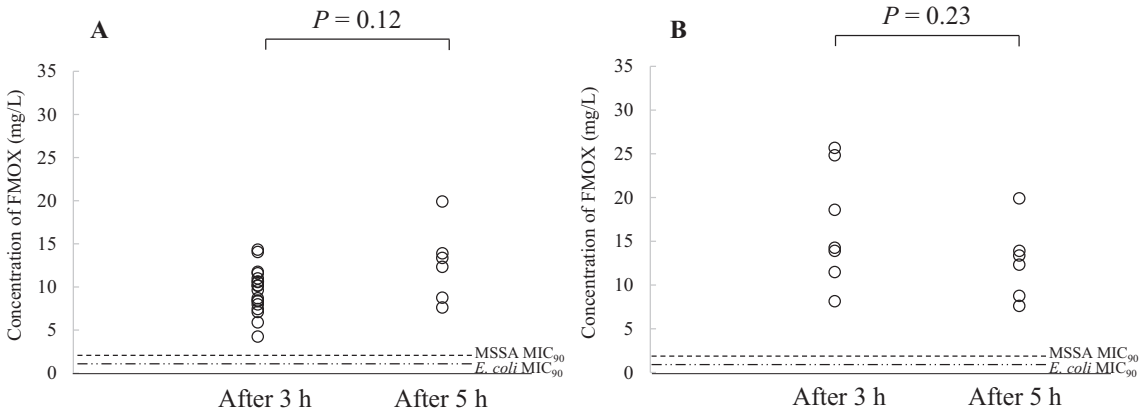

Fig. 3 Serum median FMOX concentrations compared at 3 h vs. 5 h after FMOX administration
A: Comparing 3 h (cases of Ccr >60 mL/min) vs. 5 h
B: Comparing 3 h (cases of Ccr ≤60 mL/min) vs. 5 h
FMOX: flomoxef, MSSA: methicillin-sensitive *Streptococcus aureus*, *E. coli*: *Escherichia coli*, MIC: minimum inhibitory concentration, Ccr: creatinine clearance

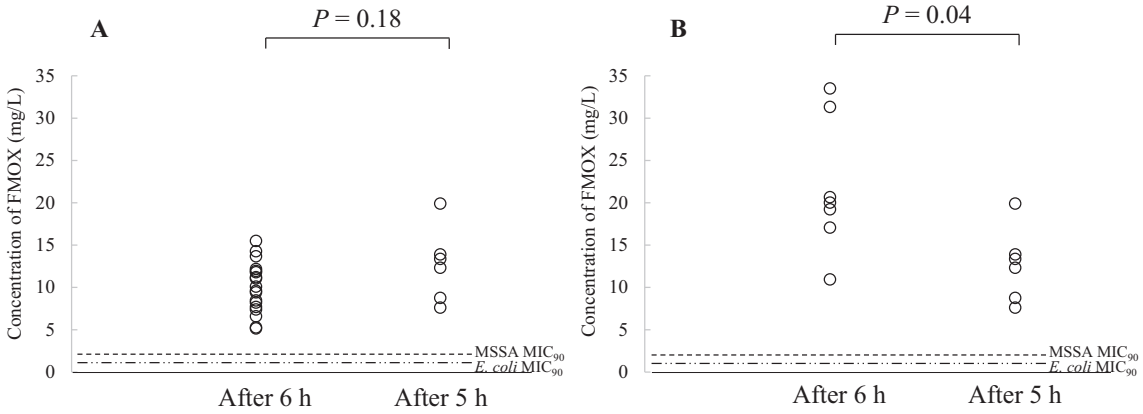

Fig. 4 Serum median FMOX concentrations compared at 6 h vs. 5 h after FMOX administration
A: Comparing 6 h (cases of Ccr >60 mL/min) vs. 5 h
B: Comparing 6 h (cases of Ccr ≤60 mL/min) vs. 5 h
FMOX: flomoxef, MSSA: methicillin-sensitive *Streptococcus aureus*, *E. coli*: *Escherichia coli*, MIC: minimum inhibitory concentration, Ccr: creatinine clearance

resistant bacteria.

Prolonged surgery necessitates additional intraoperative re-administration of prophylactic antimicrobials, considering their half-life[15,28]. Unlike cephem antibiotics, such as cefepime and ceftriaxone, with neurotoxicity as adverse effects[29,30], specific dosing intervals or adverse effects have not been outlined for FMOX. The half-life of FMOX is 1.31 h for patients with Ccr >70 mL/min and 2.48 h for those with 20 < Ccr ≤ 40 mL/min[2 22,23]. Our study demonstrated that in patients with normal renal function, sufficient FMOX concentrations could be maintained without dose elevation by redosing at intervals twice its half-life. Similarly, in patients with renal dysfunction, there was no elevation after 5 h. Our dosing interval was reasonable, considering the prolonged half-life of FMOX.

Reportedly, the incidence of SSIs in hepatobiliary-pancreatic surgery is 13.0-17.8%[25,31]. Serum concentrations of FMOX in the two cases that developed SSIs were above MIC_{90} against MSSA and *E. coli* (**Fig. 2**), suggesting that FMOX was able to maintain adequate concentrations. The two cases with SSIs were administered FMOX every 3 h. Case 1 (organ space SSIs) had a bile leak, and computed tomography showed an air-associated effusion on the incisional surface, which was suspected to be infected. Bile and drain cultures detected *Enterococcus faecalis*, which was considered the causative agent. *E. faecalis* is naturally resistant to FMOX and thus cannot be used to evaluate the adequacy of perioperative prophylaxis. Tazobactam/Piperacillin, ceftriaxone+metronidazole and

levofloxacin+metronidazole were administered to target infections, including anaerobic bacteria for a total of 20 days, and the patient showed improvement. In Case 2 (organ space SSIs), computed tomography showed encapsulated internal heterogeneous fluid accumulation around the pancreatic dissection margin. All cultures of the collected specimens were negative. The patient underwent pancreaticoduodenectomy, and although a chemical component was considered, the patient was treated with levofloxacin+metronidazole for 7 days and showed improvement. It is possible that the lesions are difficult for the antimicrobial agents to migrate to and that causative organisms not susceptible to the FMOX spectrum may have been involved.

The bleeding volume was <1,000 mL in all but one case. Case 3 with a Ccr >60 mL/min experienced significant bleeding. FMOX was administered every 3 h, resulting in a total blood loss of 10,692 mL. The FMOX concentration was assumed to have increased, especially at 9 h, and was confirmed to be high (**Fig. 2**). Despite receiving an additional dose 9 h later and transfusions, a substantial reduction in blood volume was noted between 7-11 h after the start of surgery, indicating a possible concentration and rise in FMOX levels. Tod M et al.[32] showed that plasma levels of amoxicillin and clavulanic acid were higher in patients with hemorrhagic shock than in healthy volunteers. As FMOX is a hydrophilic antimicrobial, the distribution volume dropped with hemorrhage and the serum FMOX concentration likely increased. While a statistical analysis was not conducted owing to the limited sample size, FMOX levels at the 9 h mark post-administration were observed to be roughly 1.1 times higher than at 6 h in nearly all instances. Specifically, in the case involving transfusion, the median concentration increased from 11.95 mg/L at 6 h to 14.82 mg/L at 9 h (**Fig. 2**).

The degree of protein-binding exhibited by antimicrobial agents affects various pharmacokinetic parameters, including the volume of distribution, clearance, and half-life of the drug in the blood. For FMOX, the protein-binding rate was reported to be 35%[33]. The pharmacological effects of antimicrobial agents depend on the presence of free antimicrobial agents that are not bound to proteins. When the free FMOX concentration was 65%, the medians (IQR) of free FMOX concentration at 3 h, 6 h (Ccr >60 mL/min), and 5 h were 6.42 (5.25-7.09), 6.40 (5.09-7.74), and 8.35 (6.27-8.95) mg/L, respectively, all of which exceeded the MIC_{90} values for MSSA and *E. coli*, even in the first quartile, suggesting that adequate concentrations were maintained.

It is essential to acknowledge certain limitations in the present study. First, the half-life of FMOX was prolonged in patients with Ccr <20 mL/min, although none of the patients included in this study belonged to that category. Therefore, our results may not be applicable to patients with Ccr <20 mL/min. Second, we measured total serum concentrations rather than free serum concentrations, which are typically more indicative of pharmacological effects. Although no elevation was observed at total serum concentrations, we were unable to ascertain whether elevation occurs at free serum concentrations. Finally, the present study was conducted at a single institution, and the small sample may have limited the data.

In conclusion, this study underscores the importance of precisely adjusting the FMOX dose based on renal function. In cases of normal renal function, adhering to the recommended perioperative prophylactic antimicrobial guidelines, which involve administering an additional FMOX dose every 3 h, was deemed reasonable. Furthermore, we uncovered a novel insight: for patients with impaired renal function, FMOX administration every 5 h is appropriate. Further evaluation of cases involving severe renal failure and measurement of free serum concentrations are required.

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Conflict of Interest: None declared.

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