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The Role of Nitroimidazoles in Preventing Postoperative SSI of Patients with Gastrointestinal Fistula

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Abstract

Background: The efficacy of cephalosporin plus nitroimidazole in preventing postoperative Surgical Site Infection (SSI) is unknown in Gastrointestinal (GI) fistula patients. This study was aimed to evaluate the role of nitroimidazoles in the prevention of SSI after surgery of GI fistula.

Methods: A retrospective cohort study of 165 patients undergoing surgery of GI fistula between January 01st, 2017 and December 31st, 2017 was performed. There were 43 patients receiving cephalosporins alone for prophylaxis and 122 patients receiving cephalosporins plus nitroimidazole. The primary outcome in this study was postoperative SSI and risk factors of SSI were analyzed using univariate and multivariable regression analysis. The microbiology of SSI and the incidence of other postoperative complications were also analyzed in this study.

Results: Postoperative SSI was observed in 44 patients with overall rate of 26.7%, including 21 patients with superficial SSI, 12 patients with deep SSI, and 11 patients with organ/space SSI. The incidences of overall SSI were respectively 41.9% and 21.3% in the cephalosporins alone group and cephalosporins plus nitroimidazoles group (p=0.009). The types of cephalosporins and nitroimidazoles had no impact on the incidence of SSI. The most common pathogen of SSI in this study was *Escherichia coli*. The incidences of other postoperative complications showed no significant difference between two groups.

Conclusion: The use of nitroimidazoles in prophylatic antibiotics is an effective management to reduce the incidence of postoperative SSI in GI fistula patients.

Keywords: Nitroimidazole; Surgical site infection; Gastrointestinal fistula

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Introduction

Surgical Site Infection (SSI) is the most common type of health care-associated infections according to several global survey [1,2]. The incidence of SSI is related to Human Development Index (HDI) that countries with a low HDI have a greater burden of SSI than countries with a middle or high HDI [3]. In addition, the type of surgery and class of surgical wound are the main risk factors of SSI. Gastrointestinal (GI) surgeries, especially involving the small bowel, colon, and rectum, are the highest risk procedures for development of SSI in all surgery types. GI fistula, defined as abnormal openings on the abdominal wall with concomitant leakage of GI content and commonly caused by iatrogenic injury, usually needs surgical treatments [4]. GI fistula patients who undergo surgical treatments are expected to be prone to SSI due to the class of surgical wound in fistula patients are probably dirty or infected. Moreover, GI fistula patients have some other risk factors which are reported to be related to the development of SSI, including malnutrition, long hospital stay and long-term use of broad-spectrum antibiotic [5]. We have reported that the incidence of SSI in GI fistula patients was up to 30% or more [6]. The prevention of SSI in GI fistula patients is challenging despite the rapid development of aseptic techniques and infection control practices.

Antimicrobial prophylaxis is an important management to prevent SSI in surgical patients, which has been reported to be effective for the prevention of SSI in different surgeries [7-10]. However, the selection of antimicrobial agents is still controversial. Cephalosporins are used the most widely, combined with other antibiotics or not. Anaerobic bacteria floras are the major pathogens in the gastrointestinal tract and are common pathogens that contribute to SSI after GI

surgery. The ability of cephalosporins against anaerobia is weak as we know. Recently, anaerobia play an increasingly important role in SSI as reported [11,12]. Thus, extra addition of anti-anaerobic agents in prophylactic antibiotics may be an important management to prevent SSI. Some studies have demonstrated that the risk of SSI is lower if cephalosporins are combined with metronidazole [13,14]. To date there was no study investigating the efficacy of prophylactic cephalosporin plus nitroimidazole for preventing SSI in fistula patients as we know.

We here conducted a retrospective study to compare the incidence of SSI in fistula patients receiving cephalosporin plus nitroimidazole to patients receiving cephalosporin alone. The primary objective is to investigate the efficacy of nitroimidazoles for preventing SSI. After that, the second objective is to know the microbiology of SSI and the incidence of other postoperative complications after surgery of GI fistula. These findings can act as a basis for SSI prevention in fistula patients.

Methods

Patient selection

This retrospective cohort study enrolled adult patients admitted to Jinling Hospital for surgery of GI fistula between January 01st, 2017 and December 31st, 2017. Following patients were included in our study: Patients were adult and younger than 80 years; patients were diagnosed as GI fistula according to clinical data and imaging examinations; patients underwent surgery of GI fistula. Patient exclusion criteria was as follows: Having concomitant remote infections, including skin soft tissue infections, lung infections, urinary tract infections, or catheter-related infections; receiving antimicrobial therapy within 1 week prior to surgery; receiving steroid or other immunosuppressant within 3 months prior to definitive surgery; diagnosed with severe organ dysfunctions; receiving implant placement; or diagnosed with GI fistula again after surgery. This study was approved by the ethics committees of Jinling Hospitals and performed in compliance with ethical principles of the Declaration of Helsinki.

Pathogenic examination

Samples were collected with sterile cotton swabs (Zhejiang Gongdong Medical Technology Co. Ltd., Taizhou, Zhejiang, China) and then sent to the microbiology laboratory for processing. Bacteria were isolated and then identified by the Vitek and Analytical Profile Index (API) bacterial identification systems or by traditional manual methods (BioMerieux, Hazelwood, MO, USA).

Data collection

The collected data in this study included: patient demographic data, body mass index, level of preoperative serum albumin and hemoglobin, existence of diabetes, primary diseases, type of GI fistula (single or multiple fistula), American Society of Anesthesiologists (ASA) physical status classification system (<3 points or >3 points), hospital stay before surgery, use of mechanical bowel preparation, use of oral antibiotics, site of surgery, surgery approach (open or laparoscopic surgery), volume of intraoperative blood loss (<400 ml or >400 ml), duration of surgery (<3 h or >3 h), classification of surgical wound and use of prophylactic antibiotics. The classification of surgical wound was defined according to the Center for Disease Control (CDC) criteria [15]. Considering that all patients in this study received no antimicrobial therapy before surgery, enrolled surgical wound were classified as clean-contaminated or contaminated despite intestinal contents flowing into the abdominal cavity. Prophylactic antibiotics included four cephalosporins (cefoselis, ceftazidime, ceftriaxone, and cefotaxime) without beta-lactamase inhibitors. Usage and dose of antibiotics was based on instructions and given 1 hour before skin incision. Nitroimidazole agents were ornidazole and morinidazole, 0.5 g for each time. Dose does not vary along with body weight or operation time.

Outcomes

The primary outcome in this study was the incidence of SSI, which was defined according to CDC criteria [15], including superficial incisional, deep incisional and organ-space infection. The follow-up was at least postoperative 30 days. The secondary outcomes included etiology of SSI and other postoperative complications. Microbiological culture of pus, secretion or intra-abdominal puncture fluid from the site of SSI was performed based on standard process of Jinling Hospital.

Statistical analysis

All analysis in this study was performed using SPSS 22 software. We here divided enrolled patients into two groups according to the selection of prophylactic antibiotics, group of cephalosporins and group of cephalosporins plus nitroimidazole. Continuous variables were reported as means with standard deviations and categorical variables were expressed as percentages. Comparisons of variables were performed using student tests for continuous variables and χ^2 tests for categorical variables. Variables that significantly differed between groups in univariable logistic regressions were entered into multivariable logistic regression analysis to determine risk factors of postoperative SSI. The level of significance was set at the conventional level of α=0.05. P values were two-sided and $p<0.05$ was considered statistically significant.

Results

The flow chart was shown in Figure 1. Based on inclusion and exclusion criteria, 165 GI fistula patients were enrolled finally, 43 patients in cephalosporins alone group and 122 patients in cephalosporins plus nitroimidazole group. Baseline characteristics of the patients were listed in Table 1. Patients enrolled in this study were 44.9 ± 15.5 years old. More male patients were enrolled than female patients. There were 76.4% patients suffering from single GI fistula and 87.9% patients got an ASA score of 1 or 2 points. All baseline characteristics showed no significant difference between cephalosporins alone group and cephalosporins plus nitroimidazole group.

Perioperative characteristics of patients were also collected as shown in Table 1. There was no significant difference in these variables between two groups. Most patients received mechanical bowel preparation before surgery and 59.4% patients additionally got oral antibiotics. More than half of patients suffered colon or rectum fistula and underwent colorectal resection. The 78.2% surgical wounds were classified as contaminated and the others were clean-contaminated. The most used antibiotic for prophylaxis was 4th generation cephalosporin, cefoselis, followed by ceftazidime, ceftriaxone and Cefotaxime. Average duration of antibiotic use was 5.35 ± 1.5 days.

The primary outcome, SSI, was summarized in Table 2. Overall, 44 GI fistula patients had postoperative SSI in this study and the incidence of SSI was 26.7%, including 21 (12.7%) patients with superficial SSI, 12 (7.3%) patients with deep SSI, and 11 (6.7%) patients with organ/space SSI (Table 2). In the cephalosporins

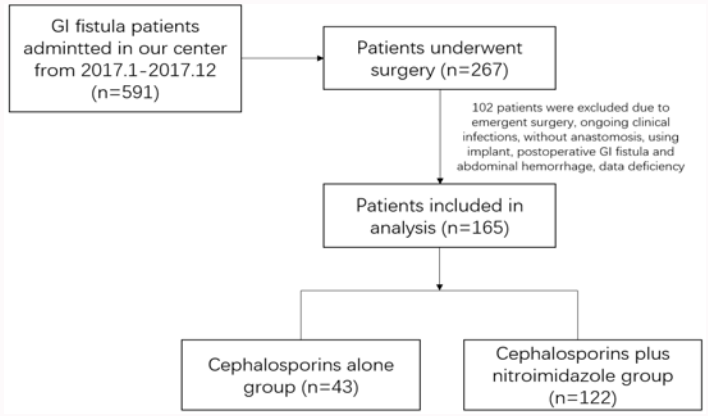

Figure 1: Patient flow chart.

Table 1: Baseline characteristics of the patients.

Variables	Total	Cephalosporins Alone	Cephalosporinsplus Nitroimidazole	P Value
Age, year	44.9 ± 15.5	43.3 ± 13.9	45.6 ± 16.0	0.317
Malegender	118	32	86	0.624
BMI, kg/m^2	19.9 ± 3.0	19.8 ± 3.5	19.9 ± 2.8	0.852
Preoperative hemoglobin, g/L	124.7 ± 19.4	124.3 ± 19.5	124.8 ± 19.4	0.868
Preoperative total bilirubin, umol/L	14.9 ± 13.2	14.9 ± 19.9	14.8 ± 9.97	0.968
Preoperative albumin, g/L	37.9 ± 5.6	37.0 ± 5.0	38.2 ± 5.8	0.238
Diabetes (%)	8 (4.8%)	2 (4.7%)	6 (4.9%)	0.944
Primary Disease (%)				
Tumor	31 (18.8%)	9 (20.9%)	22(18.0%)	0.676
IBD	26 (15.8%)	7 (16.3%)	19(15.6%)	0.913
Trauma	23 (13.9%)	6 (14.0%)	17(13.9%)	0.998
Others	85 (51.5%)	21 (48.8%)	64(52.5%)	0.683
Fistula Types (%)				
Single	126 (76.4%)	34 (79.1%)	92(75.4%)	0.627
Multiple	39 (23.6%)	9 (20.9%)	30(24.6%)	
ASA Score (%)				
<3	145 (87.9%)	38 (88.4%)	107 (87.7%)	0.908
≥ 3	20 (12.1%)	5 (11.6%)	15 (12.3%)	
Preoperative hospital stay, day	13.6 ± 10.4	15.1 ± 14.9	13.1 ± 8.3	0.53
Site of Surgery (%)				
Stomach and duodenum	2 (1.2%)	1 (2.3%)	1 (0.8%)	
Small intestine	64 (38.8%)	17 (39.5%)	47 (38.5%)	0.907
Colon and rectum	99 (60.0%)	25 (58.1%)	74 (60.7%)	0.772
Surgical Approach (%)				
Open	147 (89.1%)	37 (86.0%)	110 (90.2%)	0.456
Laparoscopic	18 (10.9%)	6 (14.0%)	12 (9.8%)	
Intraoperative Blood Loss (%)				
<400 ml	132 (80.0%)	33 (76.7%)	99 (81.1%)	0.535
≥ 400 ml	33 (20.0%)	10 (23.3%)	23 (18.9%)	
Duration Of Operation (%)				
<3 h	74 (44.8%)	22 (51.2%)	52 (42.6%)	0.333
≥ 3 h	91 (55.2%)	21 (48.8%)	70(57.4%)	

Wound Class (%)				
Clean-Contaminated	76 (46.1%)	22 (51.2%)	54 (44.3%)	0.435
Contaminated	89 (53.9%)	21 (48.8%)	68 (55.7%)	
Cephalosporins (%)				
Cefoselis	86 (52.1%)	24 (55.8%)	62 (50.8%)	0.573
Ceftazidime	44 (26.7%)	9 (20.9%)	35 (28.7%)	0.323
Ceftriaxone	20 (12.1%)	6 (14.0%)	14 (11.5%)	0.669
Cefotaxime	15 (9.1%)	4 (9.3%)	11 (9.0%)	0.955
Duration of antibiotic use, day	5.35 ± 1.5	5.2 ± 1.6	5.4 ± 1.4	0.612

Table 2: Comparisons of postoperative SSI between two groups.

Variables	Total	Cephalosporins Alone	Cephalosporinsplus Nitroimidazole	P Value
Overall SSI (%)	44 (26.7%)	18 (41.9%)	26 (21.3%)	0.009
Superficial SSI (%)	21 (12.7%)	7 (16.3%)	14 (11.5%)	0.416
Deep SSI (%)	12 (7.3%)	5 (11.6%)	7 (5.7%)	0.201
Organ/Space SSI (%)	11 (6.7%)	6 (14.0%)	5 (4.1%)	0.026

Table 3: Impacts of different types and doses of antibiotics on SSI.

Variables	Cephalosporins Alone		P Value	Cephalosporinsplus Nitroimidazole		P Value
	None-SSI	SSI		None-SSI	SSI	
Cephalosporins Type (%)						
Cefoselis	16 (66.7%)	8 (33.3%)	0.504	48 (77.4%)	14 (22.6%)	0.9
Ceftazidime	5 (55.6%)	4 (44.4%)		27 (77.1%)	8 (22.9%)	
Ceftriaxone	2 (33.3%)	4 (66.7%)		12 (85.7%)	2 (14.3%)	
Cefotaxime	2 (50%)	2 (50%)		9 (81.8%)	2 (18.2%)	
Nitroimidazoles Type (%)						
Ornidazole	-	-		43 (74.1%)	15 (25.9%)	0.243
Morinidazole	-	-		53 (82.8%)	11 (17.2%)	

alone group and cephalosporins plus nitroimidazole group, the incidences of overall SSI were 41.9% and 21.3%, respectively, showing statistical difference (P=0.009, Table 2). Separately, we compared the incidences of each type of SSI in two groups as shown in Table 2. The incidences of superficial SSI were respectively 16.3% and 11.5% in the cephalosporins alone group and cephalosporins plus nitroimidazole group and the incidences of deep SSI were respectively 11.6% and 5.7%. Both incidences showed no significant difference between two groups. On the other hand, the incidences of organ/space SSI were respectively 14% and 4.1% in the cephalosporins alone group and cephalosporins plus nitroimidazole group, showing statistical significance (P=0.026, Table 2).

We further analyzed the impacts of type and usage of cephalosporins and nitroimidazoles on the incidence of SSI as shown in Table 3. When four kinds of cephalosporins were used alone, SSI incidence showed no significant difference between patients in these groups. When combined with nitroimidazoles, these cephalosporins demonstrated similar efficacy in preventing SSI in GI fistula patients as well (P=0.900). The efficacy of two nitroimidazole agents in preventing SSI was also compared. The results demonstrated that patients using cephalosporins plus ornidazole had a SSI incidence of 25.9% and those using cephalosporins plus metronidazole had 17.2%, which showed no significant difference (P=0.243).

Risk factors were analyzed using logistic regression analysis as listed in Table 4. The factors significantly related to the occurrence of SSI were total bilirubin (≥ 17.1 umol/L), contaminated wound class and the use of cephalosporins plus nitroimidazole both in univariate and multivariate analysis.

Totally 49 patients were positive for bacterial culture and pathogens were listed in Table 5. *Escherichia coli* were the most common pathogen in all, followed by *Klebsiella pneumoniae*. The positive gram-positive pathogens were *Enterococcus faecalis* and *Enterococcus faecium*. The etiology of SSI was similar between cephalosporins alone group and cephalosporins plus nitroimidazole group.

Some other complications except SSI were also recorded in Table 6. The incidence of total complications was 7.9%, in which intestinal obstruction was the most common and five patients (3%) had intestinal obstruction. In addition, three and two patients had postoperative pneumonia and gastrointestinal bleeding, respectively. There was no significant difference in the incidence of each complication between the two groups.

Discussion

Prophylactic antibiotics are definitely an important management to prevent SSI, especially in GI fistula patients. However, the selection of antimicrobial agents is still controversial. Our study proposed that the efficacies of different cephalosporins in preventing SSI are

Table 4: Univariate and multivariable analysis of different factors associated with SSI.

Variables	Univariate		Multivariable	
	P value	OR (95% CI)	P Value	OR (95% CI)
Age (≥ 50y)	0.2	0.61 (0.29-1.31)	0.15	
Sex (male)	0.17	1.78 (0.78-4.07)	0.19	
BMI (≤ 18 kg/m^2)	0.37	0.71 (0.33-1.51)	0.35	
Hemoglobin (≤ 120 g/L)	0.26	0.66 (0.32-1.36)	0.18	
Total bilirubin (≥ 17.1 umol/L)	0.03	2.31 (1.08-4.94)	0.014	2.78 (1.23-6.32)
Albumin (≤ 35 g/L)	0.67	1.18 (0.56-2.49)	0.1	
Blood loss (≥ 400 mL)	0.52	1.27 (0.61-2.66)	0.72	
Duration of operation (≥ 3 h)	0.02	2.42 (1.16-5.08)	0.05	
Cardiovascular disease (yes)	0.76	0.83 (0.26-2.70)	0.62	
diabetes (yes)	0.44	1.70 (0.39-7.42)	0.29	
IBD (yes)	0.97	1.02(0.40-2.61)	0.1	
Malignancies (yes)	0.14	0.47 (0.17-1.31)	0.09	
History of trauma (yes)	0.13	0.37 (0.10-1.310	0.11	
Multiple fistula (yes)	0.8	1.11 (0.49-2.47)	0.59	
ASA scores (≥ 3)	0.72	1.20 (0.43-3.37)	0.78	
Colon and rectum (yes)	0.87	0.95 (0.47-1.92)	0.96	
Contaminated (yes)	0.004	2.99 (1.41-6.36)	0.002	3.53 (1.58-7.90)
Open laparotomy (yes)	0.65	1.31 (0.41-4.210	0.86	
Cephalosporins plus nitroimidazole (yes)	0.009	0.38 (0.18-0.79)	0.003	0.29 (0.13-0.66)

Table 5: Bacterial isolates cultured from SSI samples.

Variables	Total	Cephalosporins Alone	Cephalosporinsplus Nitroimidazole
Gram-Negative Bacteria (%)			
Escherichia coli	18 (36.7%)	8 (40%)	10 (34.5%)
Klebsiella pneumoniae	7 (14.3%)	2 (10%)	5 (17.2%)
Pseudomonas aeruginosa	4 (8.2%)	1 (5%)	3 (10.3%)
Morganella morganii	3 (6.1%)	1 (5%)	2 (6.9%)
Bacteroides fragilis	2 (4.1%)	1 (5%)	1 (3.4%)
Aeromonas hydrophila	2 (4.1%)	1 (5%)	1 (3.4%)
Proteus mirabilis	2 (4.1%)	2 (10%)	0 (0%)
Enterobacter cloacae	1 (2%)	0 (0%)	1 (3.4%)
Acinetobacter baumannii	1 (2%)	0 (0%)	1 (3.4%)
Gram-Positive Bacteria (%)			
Enterococcus faecalis	5 (10.2)	3 (15%)	2 (6.9%)
Enterococcus faecium	4 (8.2%)	1 (5%)	3 (10.3%)
Total (%)	49 (100%)	20 (100%)	29 (100%)

Table 6: Occurrence of other complications during hospitalization.

Variables	Total	Cephalosporins Alone	Cephalosporinsplus Nitroimidazole	P Value
Overall complications (%)	13 (7.9%)	5 (11.6%)	8 (6.6%)	0.289
Intestinal obstruction (%)	5 (3.0%)	1 (2.3%)	4 (3.3%)	0.754
Pneumonia (%)	3 (1.8%)	1 (2.3%)	2 (1.6%)	0.772
Gastrointestinal bleeding (%)	2 (1.2%)	1 (2.3%)	1 (0.8%)	0.438
Urinary tract infection (%)	1 (0.6%)	0 (0%)	1 (0.8%)	0.552
Catheter-associated infections (%)	1 (0.6%)	1 (2.3%)	0 (0%)	0.584
Cholestasis with cholecystitis (%)	1 (0.6%)	1 (2.3%)	0 (0%)	0.584

similar in GI fistula patients. When combined with nitroimidazole, prophylactic antibiotic use shows an increased ability of reducing SSI. This founding provides evidence for preoperative use of nitroimidazole for prophylaxis in GI fistula patients.

Nitroimidazoles are often used in patients undergoing abdominal surgery, especially GI surgery and the efficacy of nitroimidazoles in preventing SSI is dramatic [13,14]. Clinical practice guidelines for antimicrobial prophylaxis in surgery published in 2013 also recommend cephalosporins combined with metronidazole for prophylaxis in patients undergoing appendicectomy, surgery of intestinal obstruction and colorectal surgery [16]. Our results are the same as those of previous studies, and nitroimidazoles notably reduced the incidence of organ/space SSI. It can be explained that overflow of intestinal contents into abdominal cavity exists in patients with GI fistula and the intestinal flora will be colonized in the abdominal cavity. Anaerobic bacteria are important bacteria in the intestinal tract and the use of nitroimidazoles kills most of colonized anaerobic bacteria to reduce the incidence of SSI. Correspondingly, our study found that the most common pathogen of SSI in GI fistula patients was *Escherichia coli*, the most common aerobic bacteria in the intestinal tract, which differed from that *Staphylococcus aureus* was the most common pathogens of patients undergoing other surgery [17-19]. Culture of anaerobic bacteria is still a challenge due to their strict growth environment. It is necessary to obtain specimens according to standard process and transport specimens quickly for culture. Knowing the distribution of anaerobic pathogens of SSI is of great importance for SSI managements, however, few study investigated it to date, which may be a topic of our future research.

Four types of cephalosporins were used for prophylaxis in our study. Considering the high possibility of colonization of intestinal flora in the abdominal cavity, 3rd and 4th generation cephalosporins often are our first choice for prophylactic antibiotics, in which cefoselis was used in nearly half of enrolled patients. There was no previous study to explore the efficacy of prophylactic cefoselis in preventing SSI and our study firstly reported that cefoselis was as effective as other cephalosporins, combined with nitroimidazoles or not. As 3rd generation cephalosporins, ceftazidime, ceftriaxone and cefotaxime have similar antimicrobial spectrum. Several studies have reported that prophylactic ceftriaxone is useful for preventing postoperative SSI, showing good effectiveness and safety [20,21]. Ceftazidime is also commonly used for SSI prevention and of equivalent prophylactic efficacy to ceftriaxone [22]. Our study indicated that there was no significant difference in the efficacies of these four cephalosporins in preventing SSI. The choice of cephalosporins should base on the antimicrobial susceptibility patterns of local isolated pathogens.

Metronidazole is the most common and used nitroimidazole agents in all. However, many side effects of metronidazole have been previously reported, such as nausea, transient neutropenia, a disulfiram-like effect with alcohol and peripheral neuropathy [23]. Thus, here we utilize two nitroimidazole derivatives, ornidazole and morinidazole, to figure out the impacts of nitroimidazole agents on SSI in GI fistula patients. Ornidazole has comparable or better antibacterial properties than morinidazole [24]. Cao et al. demonstrated that morinidazole was clinically and bacteriologically as efficacious as ornidazole, while morinidazole was associated with fewer drug-related side effects than ornidazole [25]. In our study, the incidence of SSI in cephalosporins plus ornidazole group was lower than that in cephalosporins plus morinidazole group (17.2% *vs.* 25.9%). Due to small sample size, however, no significant difference was observed.

The incidences of other postoperative complications are what we focus on in this study. Overall, the incidences of other postoperative complications in GI fistula patients were at a low level and the addition of nitroimidazoles didn't increase them. This is in accord with previous study that ornidazole didn't increase the incidence of infected complications in patients undergoing elective left colectomy [26]. Zhang et al. [27] also reported that a standard dose of 500 mg morinidazole is well tolerated in patients with severe renal impairment, indicating that the safety of drugs is guaranteed.

There are some limitations in our study. First, the sample size of our study was not large enough to compare the efficacies of ornidazole and morinidazole for preventing SSI in GI fistula patients. Second, no data of anaerobic bacteria was obtained in this study, thus we cannot systematically verify the relationship between the use of nitroimidazole and SSI.

Conclusion

In summary, it can be concluded from this study that the use of cephalosporins plus nitroimidazoles is effective to reduce the incidence of postoperative SSI, especially organ/space SSI, in GI fistula patients. Both types of nitroimidazoles, ornidazole and morinidazole, have similar efficacy in preventing SSI and the addition of them won't increase the incidence of other postoperative complications.

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