TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2018) 48: 1135-1140
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doi:10.3906/sag-1804-1

Is 72 h of antimicrobial prophylaxis better than 24 h in elective gastric cancer surgery?

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Received: 01.04.2018 • **Accepted/Published Online:** 14.07.2018 • **Final Version:** 12.12.2018

Background/aim: The optimum duration of antimicrobial prophylaxis in elective gastric cancer surgery is still not yet established. The aim of this study is to evaluate the efficacy of 24 h or 72 h of antimicrobial prophylaxis for preventing postoperative infection.

Materials and methods: Between July 2016 and January 2018, 990 gastric cancer patients undergoing surgery with D2 lymphadenectomy in Ren Ji Hospital were classified into 24-h or 72-h antimicrobial prophylaxis groups. The incidence of postoperative infection complications was compared.

Results: A total of 990 patients (24-h antimicrobial prophylaxis, 708 cases; 72-h antimicrobial prophylaxis, 282 cases) were analyzed. Surgical site infection (SSI) occurred in 37 patients (5.2%) in the 24-h group and 17 patients (6.0%) in the 72-h group, respectively, and 24-h antimicrobial prophylaxis was not a risk factor for remote infection (11.2% in 24-h versus 10.2% in 72-h group). Age >60 years and pathological stage III were significantly associated with remote infection.

Conclusion: Compared to 72 h of antimicrobial prophylaxis, 24 h is not a risk factor for either SSI or remote infection. Extended antimicrobial prophylaxis might decrease remote infections for older patients or those of pathological stage III.

Key words: Gastric cancer, antimicrobial prophylaxis, surgical site infection, remote infection

1. Introduction

Gastric cancer is the fourth most common cancer and the second most frequent cause of death in the world, with curative surgery remaining the primary therapeutic approach for gastric cancer (1). Despite the great progress made in surgical skills and perioperative management during the past decades, complication rates after gastrectomy vary from 10.5% to 40.1% in different medical centers (2–6). Several studies have reported that the incidence of complications was regarded as a risk factor for gastric cancer patients' prognosis (7,8).

Postoperative application of prophylactic antibiotics is used to prevent infectious complications, such as surgical site infection (SSI) or remote infection, for clean-contaminated surgery. Patients could receive some benefits from short-term antimicrobial prophylaxis, such as reducing the development of bacterial resistance and lowering the expenses (9). The guidelines of the Centers for Disease Control and Prevention (CDC) recommend that intravenous antimicrobial prophylaxis be limited to within 24 h postoperatively (10). However, most of the previous studies comparing short-term with long-term antibiotic regimens focused on colorectal surgery (11,12) or cholecystectomy (13,14). There is not much evidence about the duration of antimicrobial prophylaxis in relation to the risk of infectious complications following curative gastrectomy with D2 lymphadenectomy. This study aims to investigate the efficacy of 24 h versus 72 h of antimicrobial prophylaxis in Chinese gastric cancer patients.

2. Materials and methods

Gastric cancer patients between July 2016 and January 2018 undergoing elective surgery at Ren Ji hospital were included in this study. The surgical procedure was potentially curable gastrectomy for cancer with D2 lymphadenectomy. Patients were excluded if they were aged less than 20 or more than 80 years, pregnant, or allergic to penicillins or cephalosporins; had received antibiotic treatment in the past 2 weeks; had perioperative infection or another organ cancer; were of ASA grade III; had a microscopic or macroscopic residual tumor, emergent surgery, moderate or severe liver disease (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, or total bilirubin more than five times the upper limit of normal), or severe renal impairment (serum creatinine level above 2.0 mg/dL); or had received preoperative chemotherapy or chemoradiotherapy and combined resection. We retrospectively reviewed medical

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histories and postoperative complications. This study was approved by Ren Ji Hospital's ethics committee.

This study was designed to investigate the efficacy of 24 h or 72 h of antimicrobial prophylaxis regimens with cefazolin or quinolones on infectious complications including SSI and remote infection. Thirty minutes before the operation both groups received 1 g of cefazolin by slow intravenous infusion over 15 min. An additional dose was administered if the operation was prolonged beyond 3 h. For 24-h prophylaxis, postoperative antibiotics were administered twice in the 24 h after the end of the surgery. For 72-h prophylaxis, postoperative antibiotics were given twice daily for 72 h. The reasons for 72-h antibiotic prophylaxis administration included age more than 65 years old, late tumor stage, prolonged operation time, or suspicion of pneumonia after the operation. The allocation was objectively dependent on patients' conditions. Perioperative management protocols and wound management were similar in both groups.

The primary endpoint was the incidence of SSI and remote infection. Determination of the presence of SSI was based on criteria developed by the CDC (10). Remote infection complications, defined as a postoperative infection at a site other than the surgical site, were defined as recommended by the Clavien–Dindo classification (15), such as pneumonia, enteritis, or urinary tract infection.

The chi-square test or Fisher's exact test was used to compare nominal variables. For comparison of continuous variables, the Mann–Whitney U test was used. A binary logistic regression model was used for multivariate analysis. Univariate and multivariate logistic regression analyses were applied to identify the factors independently influencing the risk of development of infectious complications. $P < 0.05$ was considered to denote statistical significance. Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Among the 1095 gastric cancer patients who underwent elective surgery from July 2016 to January 2018, 105 cases were excluded (combined resection n = 53, noncurative resection n = 33, neoadjuvant chemotherapy n = 6, other reasons n = 13; Figure). As summarized in Table 1, the characteristics of these 990 included patients (708 in 24-h group and 282 in 72-h group) were balanced except for age. In the 72-h prophylaxis group the mean age was 64.2 ± 11.2 years, which was significantly older than in the 24-h prophylaxis group (61.6 ± 10.9 years).

The overall number of infections was 115 in the 24-h prophylaxis group and 45 in the 72-h prophylaxis group (P = 0.912). Regarding SSI, the overall incidence was 5.5% (54 of 990 patients). The incidence of SSI was 5.2% in the 24-h prophylaxis and 6.0% in the 72-h prophylaxis group, respectively. There were no significant differences in superficial or deep incisional SSI or organ/space SSI between the two groups (Table 2). On the basis of multiple logistic regression analysis (Table 3), the odds ratios (ORs) for surgical-site infections with 72 h of antimicrobial

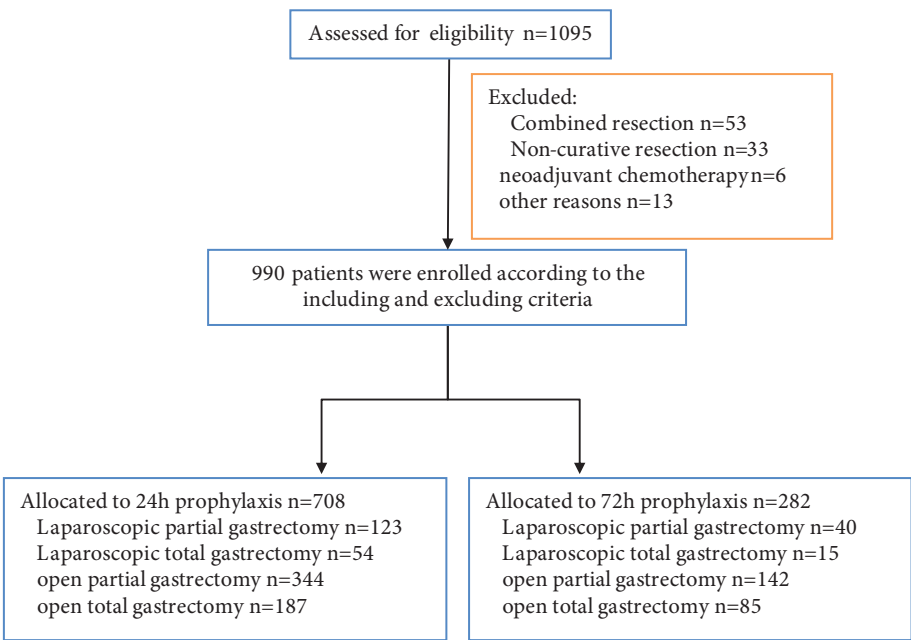

Figure. Flowchart of the presented study.

Table 1. Baseline and operative data.

	24-h prophylaxis n = 708	72-h prophylaxis n = 282	P
Age (years)*	61.6 (10.9)	64.2 (11.2)	0.008
Sex ratio (M:F)	450:258	190:92	0.076
BMI (kg/m^2)*	22.9 (9.6)	22.5 (3.4)	0.798
pT category			0.176
pT1	183 (25.8%)	75 (26.6%)	
pT2	81 (11.4%)	21 (7.4%)	
pT3–4	445 (62.8%)	186 (66.0%)	
pN category			0.474
pN0	307 (43.4%)	122 (43.3%)	
pN1	90 (12.7%)	44 (15.6%)	
pN2	134 (18.9%)	56 (19.9%)	
pN3	177 (25.0%)	60 (21.3%)	
Pathological stage			0.729
I	231 (32.6%)	86 (30.5%)	
II	63 (8.9%)	21 (7.4%)	
III	363 (51.3%)	152 (53.9%)	
IV	51 (7.2%)	23 (8.2%)	
During of operation (h)			0.920
≥4	354 (50.0%)	142 (50.4%)	
<4	354 (50.0%)	140 (49.6%)	
Estimated blood loss (mL)			0.330
≥150	96 (13.6%)	45 (16.0%)	
<150	612 (86.4%)	237 (84.0%)	
Intraoperative blood transfusion			0.535
Yes	45 (6.4%)	21 (7.4%)	
No	663 (93.6%)	261 (92.6%)	
Laparoscopy			0.065
Yes	177 (25.0%)	55 (19.5%)	
No	531 (75.0%)	227 (80.5%)	
Gastrectomy			0.671
Partial	467 (66.0%)	182 (64.5%)	
Total	241 (34.0%)	100 (35.5%)	

*Values are mean (±SD); BMI = body mass index; pT = primary tumor; pN = lymph node status.

prophylaxis were 1.03 (95% CI: 0.47–2.30) before and 1.15 (95% CI: 0.49–2.90) after adjusting for nine variables (age, sex, BMI, duration of operation, estimated blood loss, transfusions, postoperative cancer stage, laparoscopy, and open and distal or total gastrectomy)

The incidence of remote infection was 11.0% in 24-h prophylaxis and 9.9% in 72-h prophylaxis (Table 4). The rate of pulmonary infection rate was lower in the 72-h prophylaxis group but this was not significant (24-h group 9.3% versus 72-h group 7.8%). In logistic regression analysis (Table 5), the unadjusted OR for remote infection after 72 h of prophylaxis was 0.89 (95% CI: 0.51–1.56). The adjusted OR with 72 h of prophylaxis was 0.62 (95% CI: 0.31–1.27) after accounting for nine variables (age, sex, BMI, duration of operation, estimated blood loss, transfusions, postoperative cancer stage, laparoscopy, and open and distal or total gastrectomy). However, age more than 60 years (OR: 2.08; 95% CI: 1.08–3.99) and pathological stage ≥III (OR: 1.88; 95% CI: 1.02–3.48) were independent risk factors for remote infection.

4. Discussion

This retrospective study was designed to compare the incidence of SSI and remote infection in patients given antibiotic prophylaxis for 24 h with that of patients administered antibiotic prophylaxis for 72 h after elective gastric cancer surgery. It was concluded that antibiotic prophylaxis for 24 h does not increase the incidence of SSI or remote infection in gastric cancer patients.

Antibiotic prophylaxis should be effectively given for the shortest interval because extended use of antibiotics is associated with great costs and might increase the risk of adverse effects. However, controversies on the duration of antibiotic prophylaxis still exist in clinical practice (16,17). A survey in South Korea and Japan showed that at 11 institutions antimicrobial prophylaxis was routinely given for longer than 24 h after open gastrectomy (18). However, national surgical infection prevention guidelines in the United States recommend that antibiotics be discontinued within 24 h of surgery. The reason behind the longer use of antibiotics might be differences in the extent of lymphadenectomy: differing from the extended

Table 2. Incidence of surgical-site infection.

	24-h prophylaxis n = 708	72-h prophylaxis n = 282	P
Overall surgical-site infections	37 (5.2%)	17 (6.0%)	0.616
Superficial incisional	14 (2.0%)	6 (2.1%)	1.000
Deep incisional	6 (0.8%)	2 (0.7%)	1.000
Organ/space	18 (2.5%)	9 (3.2%)	0.571

D2 lymphadenectomy in East Asia (4,19), D0 or D1 lymphadenectomy was generally accepted in the United States and Europe (20,21). Most Japanese surgeons believe that the surgical stress related to gastrectomy with such lymph node dissection might deteriorate the host immune system and increase the risk of postoperative complications, including SSIs and remote infections, which might be prevented by longer antibiotic use (9).

Table 3. Univariable and multivariable logistic regression analyses for the association between risk factors and surgical-site infections.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
72-h prophylaxis	1.03 (0.47–2.30)	0.934	1.15 (0.49–2.90)	0.818
Age >60	1.27 (0.59–2.75)	0.538	1.39 (0.55–3.50)	0.492
Male sex	0.61 (0.30–1.27)	0.185	0.59 (0.25–1.37)	0.220
BMI ≥25 kg/m^2	1.10 (0.40–3.03)	0.794	1.36 (0.48–3.82)	0.562
Duration of operation ≥4 h	0.84 (0.37–1.92)	0.683	0.71 (0.29–1.78)	0.470
Estimated blood loss ≥150 mL	0.91 (0.26–3.12)	1.000	0.70 (0.20–2.52)	0.586
Intraoperative blood transfusion	1.56 (0.46–5.36)	0.729	1.03 (0.47–2.30)	0.275
Pathological stage ≥III	1.97 (0.87–4.63)	0.100	1.78 (0.63–5.05)	0.276
Open	1.55 (0.58–4.10)	0.377	0.70 (0.20–2.49)	0.581
Total gastrectomy	2.17 (1.05–4.74)	0.032	2.32 (0.97–5.57)	0.058

Table 4. Incidence of remote infection.

	24-h prophylaxis n = 708	72-h prophylaxis n = 282	P
Remote infections	78 (11.0%)	28 (9.9%)	0.617
Respiratory	66 (9.3%)	22 (7.8%)	0.448
Urinary tract	8 (1.1%)	5 (1.8%)	0.622
Enteritis	5 (0.7%)	2 (0.7%)	1.000

Table 5. Univariable and multivariable logistic regression analyses for the association between risk factors and remote infections.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
72-h prophylaxis	0.89 (0.51–1.56)	0.692	0.62 (0.31–1.27)	0.192
Age >60	2.41 (1.41–4.12)	0.001	2.08 (1.08–3.99)	0.029
Male sex	1.77 (1.06–2.99)	0.029	1.19 (0.64–2.22)	0.580
BMI ≥ 25 kg/m^2	1.16 (0.62–2.17)	0.633	1.27 (0.63–2.54)	0.509
Duration of operation ≥4 h	1.31 (0.79–2.16)	0.297	1.19 (0.66–2.15)	0.566
Estimated blood loss ≥150 mL	1.39 (0.70–2.77)	0.342	0.77 (0.31–1.90)	0.564
Intraoperative blood transfusion	1.52 (0.68–3.32)	0.429	1.08 (0.51–2.81)	0.811
Pathological stage ≥III	1.36 (0.85–2.19)	0.198	1.88 (1.02–3.48)	0.043
Open	0.86 (0.51–1.45)	0.565	0.64 (0.33–1.24)	0.187
Total gastrectomy	1.20 (0.76–1.91)	0.43	0.66 (0.35–1.26)	0.209

To date, four randomized controlled trials (RCTs) (9,22–24) have examined the optimal duration of antibiotic prophylaxis after gastric cancer surgery. Two studies recruited patients receiving various types of surgery, such as total gastrectomy, distal gastrectomy, and proximal gastrectomy with D1 + D2 lymphadenectomy; the other two studies focused on total gastrectomy and distal gastrectomy respectively with D1–D3 lymphadenectomy. They all came to the conclusion that 24 h of antimicrobial prophylaxis did not increase the incidence of SSI after gastrectomy. In this study, we focused on Chinese gastric cancer patients undergoing gastrectomy with D2 lymphadenectomy. Our findings about SSI were in agreement with those of the above studies. Regarding remote infection, Takagane et al. reported that shortened antimicrobial prophylaxis might increase the incidence of remote infection in total gastrectomy, especially pulmonary (22). In our study, 24 h of antimicrobial prophylaxis did not increase the risk of remote infections including lung, urinary tract, and enteritis infections. This result was similar to those of the other two RCTs (9,23).

Several factors are reported to be associated with SSIs, such as aging, obesity, malnutrition, prolonged operation, and combined adjacent organ resection (9,25,26). In our study, however, 24-h prophylaxis, age more than 60 years, sex, BMI, operation time, estimated blood loss of more than 150 mL, transfusion, pathological stage ≥III, open surgery, and total gastrectomy were not significant risk factors, which is in agreement with the findings of Takagane et al. (22). For remote infection, the risk factors may be different (27,28). In this study, age more than 60 years and pathological stage ≥III were significantly associated with remote infection, suggesting that advanced age and pathological stage might increase the risk of remote infection. Thus, for those patients, extended antimicrobial prophylaxis, perioperative respiratory rehabilitation, and early mobilization should be recommended to prevent remote infection (22,29).

The present study has several limitations. This retrospective research was performed at a single institution. Thus, the retrospective nature of our database may introduce inevitable bias compared to RCTs. However, data originating from a single institution avoid any interhospital variation and different perioperative managements.

The results of the current study indicate that 24-h antibiotic prophylaxis is adequate for preventing SSIs and remote infections in patients undergoing gastrectomy with D2 lymphadenectomy. However, for advanced age and pathological stage III patients, treatments such as extended antibiotics, rehabilitation, or early mobilization should be given to take precautions against remote infection.

Acknowledgments

This study was supported by the Shanghai Sailing Program, No. 17YF1415700; the Shanghai Municipal Commission of Health and Family Planning, No. 2017BR043; and the Hospital Development Center, No. 16CR2022A.

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