ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
http://dx.doi.org/10.4174/astr.2015.89.1.43
Annals of Surgical Treatment and Research

Clinical characteristics of ceftriaxone plus metronidazole in complicated intra-abdominal infection

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Purpose: Empirical antibiotics in complicated intra-abdominal infection (c-IAI), such as secondary peritonitis are a first step of treatment. Empirical antibiotic regimen is very diverse. Ceftriaxone plus metronidazole regimen (CMR) is one of the empirical antibiotic regimens used in treatment of c-IAI. However, although CMR is a widely used empirical antibiotic regimen, study regarding success, failure or efficacy of CMR has been poorly understood. This retrospective study is conducted to compare the clinical efficacy of this regimen in c-IAI according to clinical characteristics.
Methods: The subjects were patients in this hospital who were diagnosed as secondary peritonitis between 2009 and 2013. Retrospective analysis was performed based on the records made after surgery regarding clinical characteristics including albumin level, blood pressure, pulse rate, respiration rate, smoking, age, sex, body mass index, hemoglobin, coexisting disease, leukocytosis, and APACHE (acute physiology and chronic health evaluation) II score.
Results: A total of 114 patients were enrolled. In univariated analysis, the success and failure of CMR showed significant association with preoperative low albumin, old age, and preoperative tachycardia. In multivariated analysis, low albumin and preoperative tachycardia were significant.
Conclusion: It is thought that an additional antibiotic treatment plan is necessary in patients with low albumin and tachycardia when the empirical antibiotic regimen is CMR in c-IAI. Conduct of research through well-designed prospective randomized clinical study is also necessary in order to evaluate the appropriateness of CMR and decide on a proper empirical antibiotic regimen between many regimens in c-IAI based on our country.
[Ann Surg Treat Res 2015;89(1):43-47]

Key Words: Peritonitis, Ceftriaxone, Metronidazole

INTRODUCTION

Empirical antibiotics in complicated intra-abdominal infection (c-IAI), such as secondary peritonitis are a very important first step of treatment. Because several days are required for determination of c-IAI pathogen through bacterial culture, empirical antibiotics must have broad spectrum activity. However, empirical antibiotic regimen is very diverse. Several studies on diagnosis and management of c-IAI were recently reported [1,2].

Ceftriaxone plus metronidazole regimen (CMR) is one of the empirical antibiotic regimens used in treatment of c-IAI. However, although CMR is a widely used empirical antibiotic regimen, study regarding success, failure or efficacy of CMR has been poorly understood. This retrospective study is conducted to compare the clinical efficacy of this regimen in c-IAI according to clinical characteristics.

Received December 5, 2014, **Revised** January 27, 2015,
Accepted February 28, 2015

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METHODS

The subjects were patients in this hospital who were diagnosed as secondary peritonitis due to stomach perforation, small bowel perforation, and large bowel perforation between January 2009 and December 2013. Patients who were pediatrics, postoperative intra-abdominal infection, malignancy associated intra-abdominal infection, and trauma victims were excluded from this study. Peritonitis was diagnosed by preoperative abdominal computed tomography and intraoperative examination. The empirical antibiotic regimen in enrolled patients was CMR. After intravenous antibiotic treatment, oral antibiotic medications are ignored in this study.

Retrospective analysis was performed based on the records made after surgery regarding clinical characteristics including albumin level, blood pressure, pulse rate, respiration rate, smoking, age, sex, body mass index (BMI), hemoglobin, coexisting disease, leukocytosis, and APACHE (acute physiology and chronic health evaluation) II score.

Success of CMR is defined that treatment of infectious condition is completed using CMR without addition of change of other intravenous antibiotic drug. Contrarily, failure of CMR is when treatment of infection condition need to addition or change of other intravenous antibiotic drug.

SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, Chi-square test for Cross tabulation analysis and the significance was proved using Fisher exact test, P-value is less than 0.050 ($P < 0.050$) was considered statistically significant with a confidence interval of 95%. Multivariated analysis was performed using logistic regression analysis for the analysis of risk factors.

Table 1. Etiology of complicated intra-abdominal infection (n = 114)

Organ	Etiology	No. (%)
Stomach and duodenum	Peptic ulcer perforation	48 (42.1)
Small bowel	Idiopathic perforation	13 (11.4)
	Crohn disease induced perforation	4 (3.5)
	Foreign body induced perforation	1 (0.0)
Large bowel	Idiopathic perforation	28 (24.6)
	Diverticular perforation	15 (13.2)
	CFS induced perforation	5 (4.4)

CFS, colonofiberscopy.

Table 2. Characteristics of CMR success group and CMR failure group

Variable	CMR success (n = 69)	CMR failure (n = 45)	P-value
Age (yr)	58.6	69.1	<0.001
Antibiotics duration (day)	6.8	6.6	0.702
Operation time (min)	134.1	161.2	0.009

CMR, ceftriaxone plus metronidazole regimen.

RESULTS

A total of 114 patients were enrolled. The male and female ratio was 2.6:1 respectively. The age ranged between 19 years old and 92 years old and the average age was 62.3 years old. There were 48 patients of c-IAI due to peptic ulcer perforation and 18 and 48 patients had small bowel and colonic c-IAI (Table 1). Success rate of CMR was 60.5%. The average treatment period of CMR was 6.7 days. The average CMR treatment periods in the CMR treatment success group and regimen failure group were 6.8 and 6.6 days (Table 2).

In univariated analysis, the success and failure of CMR sh-

Table 3. Univariated analysis of clinical date between CMR success group and CMR failure group

Variable	CMR success (n = 69)	CMR failure (n = 45)	P-value
Age (yr)			0.019
<70	48 (69.6)	21 (46.7)	
≥70	21 (30.4)	24 (53.3)	
Body mass index (kg/m^2)			>0.999
<18	5 (7.2)	4 (8.9)	
≥18	64 (92.7)	41 (91.1)	
Albumin (g/dL)			<0.001
<3.0	11 (15.9)	22 (48.9)	
≥3.0	58 (84.0)	23 (51.1)	
Blood pressure (mmHg)			0.710
<90	4 (5.8)	4 (8.9)	
≥90	65 (94.2)	41 (91.1)	
Pulse rate			0.003
<100	49 (71.0)	19 (42.2)	
≥100	20 (29.0)	26 (57.8)	
Respiratory rate			>0.999
<30	66 (95.7)	43 (95.6)	
≥30	3 (4.3)	2 (4.4)	
Temperature (°C)			>0.999
<38	53 (76.8)	35 (77.8)	
≥38	16 (23.1)	10 (22.2)	
Hemoglobin (g/dL)			0.093
<10	10 (14.4)	13 (28.9)	
≥10	59 (85.5)	32 (71.1)	
White blood cell count (K/μL)			0.057
<12,000	42 (60.8)	19 (42.2)	
≥12,000	27 (39.1)	26 (57.8)	
Comorbidity			0.442
No	41 (59.4)	23 (51.1)	
Yes	28 (40.5)	22 (48.9)	

Values are presented as number (%).

Table 4. The result of logistic regression analysis

Variable	B	SE	Wald	*df*	P-value	Exp(B)	95% CI for Exp(B)
Albumin	1.366	0.494	7.647	1	0.006	3.919	1.489–10.320
Age	–0.749	0.477	2.468	1	0.116	0.473	0.186–1.204
Pulse rate	1.391	0.464	9.005	1	0.003	4.020	1.620–9.973
Constant	–1.027	0.443	5.386	1	0.020	0.358	-

SE, standard error; *df*, degrees of freedom; CI, confidence interval.

owed significant association with preoperative low albumin, old age, and preoperative tachycardia (Table 3). In multivariated analysis, low albumin and preoperative tachycardia were significant (Table 4).

DISCUSSION

Although primary peritonitis occurs in patients with underlying ascites from cirrhosis or nephrotic syndrome, and tuberculous peritonitis, secondary peritonitis most often arises from an enteric cause and included peritonitis following an acute perforation of the gastrointestinal tract, intestinal necrosis, postoperative peritonitis that may be secondary to an anastomotic leakage, and traumatic peritonitis [3,4].

The definition of c-IAI is used to indicate infections which, originating in an organ cavity, extend into the peritoneal space and form an abscess or peritonitis [4,5]. The definition of sepsis is systemic inflammatory response syndrome (SIRS) plus documented infection [6]. Frequently, c-IAI is accompanied by SIRS. Therefore, antibiotic treatment in the patient with c-IAI is very important and should be initiated once a patient receives a diagnosis of and intra-abdominal infection [1,7]. In our study, there were 81 patients (71%) with c-IAI with accompanying SIRS.

According to the literature, c-IAI treatment involves single regimen or combination regimen in c-IAI treatment [1,2,8]. Recommended single regimens are cefoxitin, ertapenem, moxifloxacin, tigecycline and ticarcilline-clavulanic acid. Combination regimens are cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole [1]. In addition, recommended regimen is different between mild to moderate severity and high risk severity [1]. Therefore, selection of empirical antibiotics in the patients with c-IAI is various.

However, the distinct clinical characteristics or differences of these regimens in c-IAI are poorly understood. CMR is one of the recommended regimens in c-IAI treatment [1,2,8]. CMR has been recommended in initial empirical antibiotics of c-IAI for a long time [9-11]. In our hospital, CMR has been widely used for a longtime. Therefore, this retrospective study was conducted to compare the clinical efficacy of this regimen in c-IAI according to clinical characteristics.

According to the literature, the distinction between mild to moderate severity and high risk severity is determined by several factors [12]. These factors include delay in the initial intervention, APACHE II score, advanced age, comorbidity, albumin level, nutrition status, degree of peritoneal involvement, inability to achieve adequate debriment, and presence of malignancy [1,12]. However, the definitions of the range of comorbidity and organ dysfunction, poor nutrition status, and degree of peritoneal involvement are ambiguous. Therefore, the differentiation between mild to moderate severity and high risk severity may be ambiguous.

In our study, there was no delay in the initial intervention over 24 hours. One hundred six persons had an APACHE II score within 14 points. Only eight persons had an APACHE II score over 15 points. Therefore, statistical significance in APACHE II score based on 15 points could not be evaluated because of small number.

In some reports, the success rate of CMR in c-IAI was 74.3%-91.3% [13-15]. In our study, the success rate of CMR in c-IAI was only 60.5%. Simple comparison between our results and other reported data is difficult because of differences between some studies in infection source, infection severity, country and so on. Despite this difficulty in comparison, in our result, overall success rate of CMR was low. Therefore, conduct of research through well-designed prospective randomized clinical study is necessary in order to evaluate the appropriateness of CMR in c-IAI.

The success and failure of CMR in c-IAI differed significantly different based on age (≥70). Therefore, the efficacy of CMR in c-IAI patients is poor in elderly patients (>70). Advanced age is one of the high risk or severity factors including severe physiologic disturbance and immunocompromised state [1]. Actually, elderly persons have many immunologic problems, immunocompetence condition and decline of immunologic function [16]. However, some clinicians doubt that old age is one of factors influencing antibiotic choice [8].

According to the literature, the nutritional status was determined by serum albumin level, BMI, transferrin, and weight loss [17,18]. We evaluated nutritional status using BMI and serum albumin however we could not check weight loss history. Therefore, in our study, malnutrition was determined based on serum albumin 3.0 g/dL and BMI 18 kg/m^2. The success and failure of CMR in c-IAI was significanlty different based on

the serum albumin 3.0 g/dL. However, it was not statistically significant based on the BMI 18 kg/m^2. Therefore, the efficacy of CMR in c-IAI patients with poor nutritional status based on serum albumin is poor.

In our study, the success and failure of CMR in c-IAI was significanlty different based on preoperative tachycardia (>100/min). Pulse rate is one factor of criteria in SIRS [6]. However, other factors including fever, respiratory rate and white blood cell count were not significant. In some reports, tachycardia was an independent risk factor for mortality in sepsis [19]. However, the study between pulse rate and severity of infection is poor. Therefore, it is necessary to determine relationships between pulse rate and severity of infection through well-designed clinical study.

In multivariated analysis, the change of CMR in c-IAI showed significant association with low albumin level and preoperative tachycardia. Therefore, when the empirical antibiotic regimen is CMR, an additional antibiotic treatment plan is necessary in patients with low albumin and tachycardia.

This study has some limitations. First, this study did not include a large sample size therefore, it is difficult to generalize the results. Second, the period of data collection was five years. Therefore, there was no consideration of the chronologic change in drug resistence of bacteria and endemic or epidemic bacterial pattern. Third, there was no consideration of differences regarding various hollow viscus perforations such as stomach, small bowel and large bowel. Fourth, there was no consideration of oral antibiotic medication after intravenous antibiotic treatment.

In conclusion, on the basis of our results, it is thought that an additional antibiotic treatment plan is necessary in patients with low albumin and tachycardia when the empirical antibiotic regimen is CMR in c-IAI. Conduct of research through well-designed prospective randomized clinical study is also necessary in order to evaluate the appropriateness of CMR and decide on a proper empirical antibiotic regimen between many regimens in c-IAI based on our country.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by the 2014 Yeungnam University Research Grant.

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