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

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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.

Key Words: Peritonitis, Ceftriaxone, Metronidazole
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, co-existing 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.

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 cIAI due to peptic ulcer perforation and 18 and 48 patients had small bowel and colonic cIAI (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 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) |
| Small bowel                | Crohn disease induced perforation  | 4 (3.5)  |
| Small bowel                | Foreign body induced perforation   | 1 (0.0)  |
| Large bowel                | Idiopathic perforation             | 28 (24.6) |
| Large bowel                | Diverticular perforation           | 15 (13.2) |
| Large bowel                | 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.

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)                  | 58.6                 | 69.1                 | <0.001  |
| <70                       | 48 (69.6)            | 21 (46.7)            |         |
| ≥70                       | 21 (30.4)            | 24 (53.3)            |         |
| Body mass index (kg/m²)   |                      | >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 (%).
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 cefotaxin, 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 debridement, 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/m². The success and failure of CMR in c-IAI was significantly different based on

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**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.
the serum albumin 3.0 g/dL. However, it was not statistically significant based on the BMI 18 kg/m². 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 significantly 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 multivariate 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 resistance 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.

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REFERENCES

1. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt) 2010;11:79-109.
2. Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M. et al. 2013 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg 2013;8:3.
3. Marshall JC, Innes M. Intensive care unit management of intra-abdominal infection. Crit Care Med 2003;31:2228-37.
4. Menichetti F, Sganga G. Definition and classification of intra-abdominal infections. J Chemother 2009;21 Suppl 1:3-4.
5. Solomkin JS, Mazuski JE, Baron EJ, Sawyer RG, Nathens AB, DiPiro JT, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. Clin Infect Dis 2003;37:997-1005.
6. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA. et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
7. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM. et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. 2012. Intensive Care Med 2013;39:165-228.
8. Barie PS. Surgical infections and antibiotic use. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL. editors. Sabiston textbook of surgery: expert consult premium edition: enhanced online features. 19th ed. London: Elsevier Health Sciences; 2012. p. 255.
9. Luke M, Iversen J, Sondergaard J, Kvist E, Lund P, Andersen F. et al. Ceftriaxone/metronidazole is more effective than ampicillin/netilmicin/metronidazole in the treatment of bacterial peritonitis. Eur J Surg 1991;157:397-401.
10. Bohnen JM, Solomkin JS, Dellinger EP, Bjornson HS, Page CP. Guidelines for clinical care: anti-infective agents for intra-abdominal infection: a Surgical Infection Society policy statement. Arch Surg 1992;127:83-9.
11. Park JB, Je GY, Kim SG, Jo YK. Therapeutic effects of ceftriaxone in surgical patients. J Korean Surg Soc 1986;30:727-31.
12. Swenson BR, Metzger R, Hedrick TL, McElearney ST, Evans HL, Smith RL. et al. Choosing antibiotics for intra-abdominal infections: what do we mean by “high risk”? Surg Infect (Larchmt) 2009;10:29-30.
13. Cho YK, Lee J, Suh SO, Kim SW, Jang JY, Kim SG, et al. A randomized, controlled, open, multi-center clinical trial comparing ertapenem versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections in adults. Infect Chemother 2005;37:330-6.

14. Qvist N, Warren B, Leister-Tebbe H, Zito ET, Pedersen R, McGovern PC, et al. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. Surg Infect (Larchmt) 2012;13:102-9.

15. Towfigh S, Pasternak J, Poirier A, Leister H, Babinchak T. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. Clin Microbiol Infect 2010;16:1274-81.

16. Berger DH, Dardik A, Rosenthal RA. Surgery in the geriatric patient. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston textbook of surgery: expert consult premium edition: enhanced online features. 19th ed. London: Elsevier Health Sciences; 2012. p. 335.

17. Raynaud-Simon A, Revel-Delhom C, Hebuterne X. French Nutrition and Health Program. French Health High Authority. Clinical practice guidelines from the French Health High Authority: nutritional support strategy in protein-energy malnutrition in the elderly. Clin Nutr 2011; 30:312-9.

18. Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med 1991;325:525-32.

19. Leibovici L, Gafter-Gvili A, Paul M, Almasneh N, Tacconelli E, Andreassen S, et al. Relative tachycardia in patients with sepsis: an independent risk factor for mortality. QJM 2007;100:629-34.