Five Days of Ceftriaxone to Treat Culture Negative Neutrocytic Ascites in Cirrhotic Patients

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Abstract: The goal of this study is to establish whether 5 days of ceftriaxone treatment was sufficient to cure culture-negative neutrocytic ascites in cirrhotic patients. We studied 50 cirrhotic patients with culture-negative neutrocytic ascites. All were treated with ceftriaxone, 1.0 g IV, twice a day for 5 days. A control paracentesis was performed 48 hours after starting the therapy to assess response to the treatment. A total of 17 demographic, clinical, and laboratory variables were recorded in all cases on the day of diagnosis of CNNA. The mean age of the patients was 57.7 ± 13.2 years. Thirty-two patients were males and 18 females. The etiology of cirrhosis was hepatitis C virus in 20 patients (40%), hepatitis B virus in 16 patients (32%), cryptogenic in 13 patients (26%), and alcohol abuse in 1 patient (2%). Eighty percent of the patients were in Child–Pugh Class C. Resolution rate of culture-negative neutrocytic ascites on day 5 of treatment was 78%. Hospital mortality in cirrhotic patients with culture negative neutrocytic ascites was 4%. Statistical analysis showed that none of the 13 selected variables as covariates significantly related with the resolution of culture-negative neutrocytic ascites. Five days of ceftriaxone treatment is an adequate therapy for culture-negative neutrocytic ascites.

Key Words: culture negative neutrocytic ascites, ceftriaxone, cirrhosis

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Culture-negative neutrocytic ascites (CNNA) is a variant of ascitic fluid (AF) infection. The clinical, prognostic, and therapeutic characteristics of CNNA are reported as similar to that of spontaneous bacterial peritonitis (SBP).[1–4] Third generation cephalosporins are accepted as effective antibiotics in the treatment of SBP.[1–8] A recent consensus document about SBP has recommended a minimum duration of 5 days of antibiotic therapy with third-generation cephalosporins[3].

In this study, we report our data on the treatment of CNNA with a 5-day course of ceftriaxone, a third generation cephalosporin.

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PATIENTS AND METHODS

Two hundred and seventy-two episodes of SBP seen at Erciyes University Hospital between January 2001 and January 2002 were evaluated. Among these, 50 patients (18.3%) with CNNA were included in the study; 23 of 50 patients had the first episode of CNNA and 27 of 50 had at least one episode of SBP or CNNA before. The diagnosis of cirrhosis was confirmed by clinical, biochemical, abdominal ultrasonography, and pathologic findings. The diagnosis of CNNA was established according to the following criteria: AF with polymorphonuclear (PMN) count of more than 250 cells/mm^3 and the absence of clinical, biologic, or radiologic findings suggestive of secondary peritonitis. Other possible causes of neutrocytic ascites such as peritoneal carcinomatosis, pancreatitis, tuberculosis, hemorrhage into the AF and previous antibiotic treatment were ruled out.[1–4] An aliquot of AF was tested for total protein, albumin, PMN count and bacterial culture. We inoculated 10 mL of AF directly into each blood-culture bottle (aerobic and anaerobic media) at the bedside.[9] Serum-ascites albumin gradient was 1.1 g/dL or higher in all cases. We treated all patients with SBP with ceftriaxone (IV, 1.0 g twice daily); afterward culture negative patients were enrolled in the study and completed the treatment five-day treatments. We performed a control paracentesis after 48 hours of therapy to assess response to treatment and to determine if there was any need to modify antibiotic therapy or to initiate investigations to rule out secondary peritonitis.[1,2,6] Patients who had a reduction in the PMN count of AF more than 25% in relation to the pretreatment values after 2 days of antibiotic therapy were accepted as probable responders to the treatment.[3,10] A third paracentesis was performed on the 5th day of treatment. CNNA was considered cured when all clinical signs and symptoms of infection disappeared and ascitic fluid PMN count showed less than 250 PMN cells/mm.[31,3,4] If more than 250 cells/ mm^3 were present antibiotic was changed empirically[3] to norfloxacin and these patients were accepted as nonresponders to ceftriaxone treatment.

Seventeen variables were recorded at the time of diagnosis of CNNA (Tables 1 and 2). Thirteen variables: age, gastrointestinal hemorrhage, encephalopathy, AF variables (polymorphonuclear count, and total protein), serum leukocyte

TABLE 1. Clinical Data of Patients with CNNA

Variable	n (%)
Age (years ± SD)	57.7 ± 13.2
Sex (M/F)	32/18
Etiology	
HCV	20 (40%)
HBV	16 (32%)
Cryptogenic	13 (26%)
Alcohol abuse	1 (2%)
Gastrointestinal hemorrhage	6 (12%)
Hepatic encephalopathy	14 (28%)
Fever, abdominal pain, tense ascite	30 (60%)
Child-Pugh classification	
Class B	10 (20%)
Class C	40 (80%)
CNNA resolution on Day 5	39 (78%)
Hospital mortality	2 (4%)

count, serum total bilirubin, serum albumin, prothrombin time, serum urea, serum creatinine, serum sodium, and Child–Pugh classification were selected as covariates in binary logistic regression analysis to identify the effect of variables on CNNA resolution. Results are presented as mean ± SD. Reported *P* values are two-tailed. Values of less than 0.05 were considered as statistically significant. Erciyes University medical faculty ethical committee approved study protocol. Informed consent was obtained from the patients prior to the study.

RESULTS

Of the 50 patients that were studied, 32 were males and 18 females. The mean age was 57.7±13.2 years. The cause of cirrhosis was hepatitis C virus in 20 patients (40%), hepatitis B virus in 16 patients (32%), cryptogenic in 13 patients (26%), and alcohol abuse in 1 patient (2%). Forty patients (80%) were in Child–Pugh class C. Hepatic encephalopathy was present in 14 (28%) and gastrointestinal hemorrhage was present in 6 (12%) patients.

TABLE 2. Laboratory Data of Patients with CNNA

Variable	Mean ± SD
Ascitic fluid	
Leukocyte count (cells/mm^3)	1799.4 ± 1646.8
PMN leukocyte (cells/mm^3)	1259.4 ± 1409.5
Total protein (mg/dl)	1.63 ± 1.23
PMN leukocyte (cells/mm^3 (48th h)	781.16 ± 1108.9
Serum	
Leukocyte count (cells/mm^3)	10116.8 ± 9700.6
Total bilirubin (mg/dl)	5.4 ± 8.0
Albumin (mg/dl)	2.98 ± 0.67
PT (s)	19.7 ± 6.6
BUN (mg/dl)	27.5 ± 18.8
Creatinine (mg/dl)	1.1 ± 0.9
Sodium (mEq/l)	137.40 ± 5.83

AF polymorphonuclear count was diminished by 25% or more 48 hours after the treatment in 35 patients (70%). However 5 of 35 patients (14%) who were considered as probable responders had more than 250 cells /mm^3 in AF on the 5th day of treatment. Remaining 15 patients whose AF PMN count did not reduce more than 25% on the second day of treatment were considered as probable non-responders. Nevertheless, 9/15 (60%) of those patients responded to the treatment on 5th day of treatment. CNNA resolution on day 5 of treatment was achieved in 39 patients (78%). Hospital mortality was 4% (2 patients) in cirrhotic patients with CNNA. The causes of death were gastrointestinal bleeding in one and liver failure in the other. When all 272 episodes of SBP were taken into account, 6 patients (2.21%) died.

Among the 13 variables analyzed (age, gastrointestinal hemorrhage, encephalopathy, serum leukocyte count, serum total bilirubin, serum albumin, prothrombine time, serum urea, serum creatinine, serum sodium, Child–Pugh classification, and AF variables such as polymorphonuclear count and total protein) none were found as related to CNNA resolution ($P > 0.05$; binary logistic regression analysis).

DISCUSSION

We planned this study to reveal whether 5 days of ceftriaxone therapy was sufficient to resolve CNNA in cirrhotic patients and also to observe the importance of control paracentesis at the 48th hour of treatment.

Any of the selected factors were not found significantly correlated with the resolution of CNNA on binary logistic regression analysis in this study.

Our results confirmed that 5 days of ceftriaxone treatment was adequate to treat CNNA. We also noted that 25% decrease of ascitic fluid PMN count was detected in control paracentesis in 70% of patients. On the other hand, when end-treatment results on the 5th day were taken into account, 5 of 35 patients (14%) who were previously judged as responders became non-responders whereas 9 of 15 patients (60%) who were previously judged as non-responders became responders.

In the light of these data, control paracentesis after 48 hours from initiation of the treatment may give an idea about the effectiveness of the treatment however, unless an additional pathology such as secondary bacterial peritonitis intervenes during this period, initial treatment regimen should not be changed.[3,4]

Although hospital mortality of spontaneous bacterial peritonitis was reported as 90% in early studies it is reduced to approximately 20% with early recognition of the disease,

prompt and appropriate antibiotic therapy.[4] Appropriate antibiotic must be used because cirrhotic patients are prone to develop nephrotoxicity and super infections.[1–4] In this study it is determined that a 3rd generation non-nephrotoxic antibiotic, ceftriaxone is effective in treating CNNA and no side effects developed during the course of the treatment.

Even though hospital mortality was reported about 20% in cirrhotic patients with SBP,[4] our hospital mortality rate in cirrhotic patients with CNNA was 4%. Mortality causes were uncontrolled variceal bleeding and liver failure in our cases. Therefore it can be accepted that CNNA is not a major cause of mortality if it is properly treated. This is not a confusing result because in a recent paper, Such and Runyon[1] reported that there were essentially no deaths as a result of SBP if SBP was detected and treated before the development of shock or renal failure.

In conclusion, present results confirm that a 5-day course of ceftriaxone is an effective regimen for treating CNNA.

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